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*Editorial*

# H2 receptor antagonists and gastrointestinal cancer

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Histamine type-2 receptor antagonists have been used extensively in the past for the treatment of peptic ulcer. It has been also reported that they are implicated in a positive way in the better outcome of patients suffering from gastrointestinal cancer. Most of the experiments conducted during the last fifteen years compared the efficacy of various H2-receptor antagonists and tried to elucidate the mechanism of their alleged anticancer action. The results of these studies showed that only cimetidine, among the rest of the drugs of this category, exhibited such an action, mainly via its immunomodulating effect, exerted along several different pathways, all leading to the enhancement of the cell-mediated immune response.

The work of Gifford & Tilberg (1987) is the first demonstration that histamine type-2 receptor antagonists are capable of increasing IL-2 production after lymphocyte activation.[1]

It is well known, that IL-2 is the most potent growth factor and activator of T lymphocytes and induces the release of mediators such as IFN-γ. It also exerts its action on the large granular lymphocytes (LGLs) and on B lymphocytes, induces proliferation and differentiation and activates macrophages. The first and most substantial step of the T cell activation is the recognition of the foreign antigen on the surface of an antigen-presenting cell (e.g. macrophage). This signal activates a subgroup of T cells, leading them to express a high affinity receptor for IL-2 on their surface. At the presence of IL-2 this subpopulation proliferates, resulting in clonal expansion of other cell subpopulations, which, in turn, are capable of mediating a number of activating, suppressing and cytotoxic actions. IL-2 also stimulates natural killer cells (NK), giving rise to lymphokine-activated killer cells (LAKs). Thus, cimetidine increases the ability of IL-2 to activate a number of cells capable of exerting a cytotoxic effect on cancer cells, by increasing its production by T lymphocytes.

Perioperative administration of cimetidine to patients undergoing colonic resection for carcinoma significantly increased the number of tumor-infiltrating lymphocytes (TIL) and was correlated with a trend toward improved survival at 3 years, as was shown in the study of Adams and Morris (1997).[2] The presence of TIL within colorectal carcinomas has been found to be an independent predictor of a better prognosis. It is likely that those lymphocytes found within the primary carcinoma represent clonal expansion of one or more populations of lymphocytes that recognize particular tumor-associated antigens. The presence of such a population of cells may then lead to a long-term survival benefit by the recognition and neutralization of occult metastatic disease remaining after resection of the primary tumor.

Tumor growth and metastatic disease are associated with the advent of host suppressor cells, which undermine what would otherwise be an effective anti-tumor immune response. One characteristic of suppressor cells is the presence on their surface of a receptor for histamine of the H2 type. Histamine is a potent activator of suppressor cells. The study of Osband et al (1981) and Sahasrabudhe et al (1986) showed that cimetidine effectively inhibits suppressor T-cell function (Ts) by blocking this H2-type receptor and, thus, enhances the immune response against cancer.[3,4]

The results of a recent study by Kubota et al (2002), suggest that cimetidine may also enhance the host's antitumor cell-mediated immunity by improving the suppressed dendritic cell (DC) function of advanced cancer patients.[5]

Dendritic cells, which are potent antigen presenting cells capable of priming naove T lymphocytes and subsequently inducing cytotoxic T lymphocytes (CTL) by

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stimulation of Th1 type immune response, play a central role in cell-mediated immunity. Moreover, DCs stimulate NK cell activity.

Cimetidine, via an unknown mechanism, and not via H2 receptors, increases the antigen presenting capacity of dendritic cells, as seen by the reactions of [$^3$H]thymidine incorporation by allogeneic mixed lymphocytes. It does, however not exert, any enhancing effect on differentiation of dendritic cells in cancer patients. In the same study, cimetidine increased the production of IL-12 by the DCs in colorectal cancer patients (which is well-known to lead CD4+ helper T lymphocytes to induce Th1-type immune responses) to levels similar to those of normal controls, in this way, significantly improving, DC function, which is definitely impaired in cancer patients.

In addition to the immunomodulatory effect on gastrointestinal cancer, cimetidine seems to be beneficial to survival in cancer, acting in ways involving cell adhesion and the metastatic potential of the primary tumor. Recently, Kobayashi et al (2000) demonstrated for the first time, that cimetidine can block the adhesion of a colorectal cell line to the endothelial cell monolayer in cell culture and that it can suppress the metastasis of the tumor cell in a nude mouse model.[6]

The adhesion of cancer cells to vascular endothelial cells is a key step in invasion and metastasis. This procedure is mediated by the sialyl Lewis-X (sL$^x$) and sialyl Lewis-A (sL$^a$) antigens, which are expressed on cancer cells and are ligands to E-selectin. Tumors expressing sLx and sLa antigens at higher levels show a markedly higher frequency of metastasis and a significant lower survival rate, thus being more aggressive. E-selectin (or ELAM-1) is a member of the selectin family of adhesion molecules and is expressed on activated endothelial cells and on the surface of tumor endothelial cells. Matsumoto et al (2002) proved that treatment with cimetidine markedly reduced the incidence of metastasis and increased survival in patients whose tumor cells expressed sL$^x$ and sL$^a$ epitopes at increased levels, but not in those with low levels.[7] The effect of cimetidine does not appear to be at the level of E-selectin gene expression, because the E-selectin protein level was reduced without significantly reducing its mRNA level. Moreover, cimetidine failed to block NF-$\varkappa$B nuclear translocation. The action of cimetidine on E-selectin expression seems to involve a step after transcription, probably by interfering with signalling mediators, such as p38 MAPK, which activates the expression of a number of genes at the level after transcription.

Despite these optimistic studies concerning the beneficial effect of H2-receptor antagonists and, in particular, cimetidine, on the better outcome of patients with GI cancer, there are several other studies which doubt it.[8,9]

It is therefore necessary fpr further studies to be conducted, in order to come to any solid conclusions, especially on clinical ground.

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