Câncer e Cimetidine: anti-proliferativo, anti-angiogênico, anti-metastático, apoptótico e estimulante da imunidade celular

01/02/2009

José de Felippe Junior

"Na arte de curar, deixar de aprender é omitir socorro e retardar tratamentos esperando maiores evidências científicas é ser cientista e não médico"
JFJ

"Em primeiro lugar sempre a Medicina Convencional"
JFJ

"Se a Medicina Convencional não surtiu os efeitos desejados temos o direito e o dever como médicos de utilizar os recursos da Medicina Complementar"
Declaração de Helsinki

"Nunca devemos trocar a Medicina Convencional pela Medicina Alternativa podemos sim complementar ambas com Estratégias bem estudadas da Medicina Complementar"
JFJ

"Na verdade a MEDICINA é uma só"
Vários Autores

"É do médico a responsabilidade do paciente"
Declaração de Helsinque

"Curar muitas vezes, aliviar e consolar sempre, desistir nunca"
Médicos Humanos

"O fundamento mais profundo da medicina é o amor"
Paracelso

"A saúde é a primeira das liberdades"
Amiel

A cimetidina é um dos mais populares e mais estudados antagonistas do receptor H2 tendo surgido em 1970 para tratar úlceras gastroduodenais e gastrites.

Muitos autores verificaram que a cimetidina pode funcionar como anti-proliferativo, anti-angiogênico, anti-metastático, apoptótico e estimulante da imunidade celular nos pacientes com câncer gástrico, colo-retal, tumor de glândulas salivares, carcinoma hepático e renal, melanoma e glioblastoma .

Alguns pesquisadores notaram melhora das condições clínicas, mas não na sobrevida com o uso da cimetidina no pós-operatório de cirurgia de tumor colo-retal.

A cimetidina inibe a ligação da dehidrotestosterona no receptor andrógeno e diminui levemente o risco de câncer de próstata em estudo que envolveu 48.512 homens estudados por 17 anos. Somente o uso diário de cimetidina por 10 anos seguidos aumentou o risco de câncer de próstata em estudo envolvendo 33.506 pacientes entre 50 e 70 anos.

A cimetidina inibe a hidroxilação do estradiol e aumenta a secreção de prolactina ,porém não interfere na incidência do câncer de mama.

A cimetidina é mais um medicamento que podemos utilizar no tratamento coadjuvante de qualquer tipo de câncer ao lado da estratégia de estruturação da água intracelular.

Efeitos da cimetidina no câncer

1. Anti-metastático
    1. diminui a expressão da E-caderina induzida pelo 5-Fluoracil
    2. inibe a migração das células do hepatocarcinoma por diminuir o AMPc
    3. antagoniza a IL-1 e inibe a E-selectina no hepatoma
    4. inibe a E-selectina independente do seu efeito antagonista da histamina
    5. diminui a expressão do NCAM – "neural cell adhesion molecule" - nas glândulas salivares.
2. Anti-angiogênico
    1. diminui a produção endotelial do "Vascular-Like-Tube" (VLT)
    2. inibe o fator de crescimento endotelial (EGF) por diminuir o AMPc
3. Anti-proliferativo
    1. antagoniza o efeito proliferativo da histamina
    2. diminui a atividade da glutationa S-transferase
    3. bloqueia NCAN nas glândulas salivares
4. Indutor da apoptose
    1. ativa caspases 3,7,8 e 9 nas glândulas salivares por diminuir a expressão da NCAM
5. Imunoestimulante
    1. aumenta o número de linfócitos T intratumoral
    2. aumenta CD4 no sangue
    3. aumenta neutrófilos no sangue
    4. aumenta a atividade das células "Natural Killer" no baço

5. aumenta a produção de IL-18 pelos monócitos via ativação da caspase-1 e do aumento do AMPc o que ativa a proteína-kinase A (PKA).

Resumo de alguns trabalhos científicos

Cimetidine inhibits angiogenesis and suppresses tumor growth
Biomed Pharmacother. 2005 Jan-Feb;59(1-2):56-60
Natori T, Sata M, Nagai R, Makuuchi M.
Cimetidine, a histamine type-2 receptor antagonist, has been reported to improve survival of patients with cancers. However, the exact mechanisms by which cimetidine suppresses development of cancers remain to be elucidated. Solid tumors require neovascularization for their growth. Here, we investigated the effects of cimetidine on tumor growth and angiogenesis. Syngeneic colon cancer cells, CMT93 cells, were inoculated into the subcutaneous space of C57BL/6 mice. Mice were treated with either saline or cimetidine. Tumor size was measured everyday and angiogenesis was evaluated histologically. Cimetidine markedly suppressed tumor growth with reduced neovascularization in the tumor. Cimetidine had no effect on proliferation of CMT93 cells in vitro. Vascular endothelial growth factor production by cancer cells was not affected by cimetidine, while vascular-like tube formation by endothelial cells in vitro was significantly impaired in the presence of cimetidine. Our findings suggest that cimetidine suppresses tumor growth, at least in part, by inhibiting tumor-associated angiogenesis.PMID: 15740937

Effects of perioperative cimetidine administration on peripheral blood lymphocytes and tumor infiltrating lymphocytes in patients with gastrointestinal cancer: results of a randomized controlled clinical trial
Hepatogastroenterology. 2005 Mar-Apr;52(62):504-8.
Li Y, Yang GL, Yuan HY, Bai DJ, Wang K, Lin CR, Hu MB, Feng MH.
BACKGROUND/AIMS: Cimetidine (CIM) seems to have positive effects on the immune systems of cancer patients. This study was conducted to investigate the effects of perioperative administration of CIM on the peripheral blood lymphocytes, natural killer (NK) cells and tumor infiltrating lymphocytes (TIL) in patients with gastrointestinal (GI) cancer. METHODOLOGY: Forty-nine GI cancer patients were randomized into a treatment group which took CIM in the perioperative period, and a control group which did not take the drug. The treatment was initiated 7 days (d) before operation and continued until 10 d after surgery. At baseline examination, before operation, on the 2nd and the 10th postoperative d, peripheral blood T lymphocytes, helper T cells, T suppressor cells, and NK cells were measured by immunocytochemical method. The surgical specimens were examined for TIL response, and immunohistochemical study was performed to measure the proportion of T and B lymphocytes in the TIL population. RESULTS: In comparison with normal controls, both the treatment and the control groups had decreased T cells, helper T cells and NK cells at baseline. In the control group, total T cells, helper T cells and NK cells declined progressively with the disease course and the decreases became more profound after operation. From the baseline to the 2nd postoperative d, the proportion of total T cells, helper T cells, and NK cells went down from 60.5+/-4.6 to 56.2+/-3.8 percent, from 33.4+/-3.7 to 28.1+/-3.4 percent, and from 15.0+/-2.8 to 14.2+/-2.2 percent, respectively. On the other hand, there were significant improvements in these parameters after CIM treatment. On the 10th postoperative d, the treatment group had significantly higher percentages of total T cells, helper T cells and NK cells than control group. Moreover, CIM treatment also boosted the TIL response, as was reflected by findings that 68% (17/25) of the patients in the treatment group had significant TIL responses and only 25% (6/24) of the cases had discernible TIL response. CONCLUSIONS: Perioperative application of CIM to GI cancer patients could help restore the diminished cellular immunity boost TIL responses to tumor.PMID: 15816467

The effect of cimetidine mainly increases CD4+ cells of peripheral blood T lymphoytes
Gan To Kagaku Ryoho. 2005 Oct;32(11):1576-7
Asakage M, Tsuno NH, Kitayama J, Yamada J, Tsuchiya T, Yoneyama S, Takahashi K, Nagawa H.
Cimetidine, one of the most popular histamine-2 receptor antagonists, has been reported to improve survival in gastrointestinal cancer patients and to activate cell-mediated immune response in surgical patients. NKT cells are a population of T cells that share characteristics with natural killer cells, and their main functions are production of immunoregulatory cytokines and cytolytic activities. In this study, we aimed to investigate the effect of cimetidine on the cell-mediated immunoresponse. Six healthy adult volunteers were given 800 mg of cimetidine per day orally, and their blood samples were taken prior to and at days 1, 3, 5, and 7 days post-administration of cimetidine. Leukocyte counts and differentials were obtained by the conventional hemogram, and the leukocyte subsets were analyzed by flow cytometry. Cimetidine administration caused leukocytosis, dependent on the increase of neutrophils, as well as of the CD3-positive T lymphocytes, and the subset of CD4-positive cells among them. On the other hand, the NK cell subpopulation was decreased, and the NKT cell subpopulation was not affected. The present results suggest that cimetidine is a modulator of the cellular immunity, and may be used as the activator of the tumor specific immunoresponse.PMID: 16315874

Cimetidine inhibits in vivo growth of human colon cancer and reverses histamine stimulated in vitro and in vivo growth.
Gut 1994;**35**:1632-1636;
W J Adams, J A Lawson, D L Morris
The effect of histamine and cimetidine on the growth of four human colon cancer cell lines was studied. Histamine significantly stimulated the uptake of tritiated thymidine in vitro in a dose dependent manner, to a maximum of 120% and 116% of controls for C170 and LIM2412, respectively. This effect was antagonised by cimetidine, but not diphenhydramine. Histamine also stimulated a dose dependent increase in cyclic adenosine monophosphate accumulation in C170 cells, antagonised by cimetidine. When grown as subcutaneous xenografts in Balb/c nu/nu mice, cimetidine had a significant inhibitory effect on the same two cell lines. The final volume of C170 tumours in animals given cimetidine was 44% of controls. This response was dose dependent, plateauing at a cimetidine dose of 50 mg/kg/day. The final volume of LIM2412 tumours in animals given cimetidine was 60% of controls. Histamine administered locally by a mini-osmotic pump stimulated C170 tumour growth to 164% of controls, was antagonised by cimetidine at a dose of 200 mg/kg/day, but not by lower concentrations. Histamine has a trophic effect on at least two colorectal cancer cell lines in vivo and in vitro. As this effect is antagonised by cimetidine, it may be mediated via tumour histamine type 2 receptors.

Effect of cimetidine on E-selectin expression on the vascular endothelium stimulated by anti-cancer drug
Gan To Kagaku Ryoho. 2007 Nov;34(12):1902-4
Kawase J, Kobayashi K, Imaeda Y, Umemoto S, Ozawa S, Matsumoto S.
Various anticancer drug treatments have contributed to elongating survival of cancer patients. However, cancer often metastasizes and recurs in spite of anti-cancer drug treatment. It is important to control metastasis in order to achieve a favorable outcome. In this study, we confirmed that an expression of E-selectin in human umbilical vein endothelial cells (HUVEC) was stimulated by 5-FU, and that the expression of E-selectin was inhibited by cimetidine which was a H2 receptor antagonist. PMID: 18219847

Anti-tumor effects of cimetidine on hepatocellular carcinomas in diethylnitrosamine-treated rats
Oncol Rep. 2008 Feb;19(2):361-8.
Furuta K, Sato S, Miyake T, Okamoto E, Ishine J, Ishihara S, Amano Y, Adachi K, Kinoshita Y.
Cimetidine is known to have an anti-tumor effect on certain types of malignancies, though on hepatocellular carcinomas (HCCs), its

effect remains unclear. We studied the anti-tumor effects of cimetidine on chemically-induced HCCs in rats. Four-week-old male Wistar rats (n=105) were divided into 4 groups. Those in groups A and B were administered diethylnitrosamine (DEN) intraperitoneally at 100 mg/kg body weight every week for 6 weeks, during which rats in group A were given tap water and those in group B received cimetidine (100 mg/kg/day) in their drinking water. Rats in groups C and D were administered saline instead of DEN and given tap water with 100 mg/kg/day of cimetidine, respectively. The animals were sacrificed at 7, 12, 22 and 32 weeks after the first administration of drugs and examined. Liver nodules were observed only in groups A and B, with the number of nodules, maximum diameter of the largest nodule, and liver weight significantly lower in group B. Immunohistochemistry findings showed that glutathione S-transferase placental-positive preneoplastic foci were significantly decreased in group B. Cimetidine treatment decreased the number of proliferating cell nuclear antigen-positive hepatocytes and tended to enhance natural killer (NK) cell activity in splenic lymphocytes. In addition, flow cytometry revealed that the proportion of NK cells among total splenic lymphocytes was not affected by cimetidine treatment. Our results showed that cimetidine has an inhibiting effect on hepatocarcinogenesis.PMID: 18202782

Cimetidine inhibits epidermal growth factor-induced cell signaling J Gastroenterol Hepatol. 2007 Mar;22(3):436-43.
Fujikawa T, Shiraha H, Nakanishi Y, Takaoka N, Ueda N, Suzuki M,

BACKGROUND: Cimetidine, a histamine-2 (H2) receptor antagonist, has been demonstrated to have anticancer effects on colorectal cancer, melanoma and renal cell carcinoma. In the current study, we clarified that cimetidine inhibits both epidermal growth factor (EGF)-induced cell proliferation and migration in hepatocellular carcinoma (HCC) cell lines. METHOD: HCC cell lines (Hep3B, HLF, SK-Hep-1, JHH-2, PLC/PRF/5 and HLE) were used and cell proliferation was assessed by [3H]-thymidine incorporation assay. Cell migration was measured by in vitro cell migration assay. Biological effects of cimetidine were assessed with human EGF receptor (EGFR)-expressing mouse fibroblast cells (NR6-WT). The autophosphorylation of EGFR and the activation of other downstream effectors were analyzed by immunoprecipitation and immunoblotting. The concentration of intracellular cyclic AMP (cAMP) was measured by competitive enzyme immunoassay. RESULTS: Cimetidine inhibited both EGF-induced cell proliferation and migration in Hep3B, HLF, SK-Hep-1 and JHH-2, while cimetidine did not affect EGF-induced cell proliferation and migration in PLC/PRF/5 and HLE. Cimetidine was revealed to disrupt the EGF-induced autophosphorylation of EGFR and its downstream effectors, mitogen activated protein kinases and phospholipase C-gamma. To define the molecular basis of this negative regulation, we identified that cimetidine significantly decreased intracellular cAMP levels and that decrement of cAMP inhibited autophosphorylation of EGFR. The cell permeable cAMP analog, CPT-cAMPS reversed the cimetidine-induced inhibition of EGF-induced cell proliferation and cell migration by restoring autophosphorylation of EGFR. CONCLUSION: Cimetidine inhibited EGF-induced cell proliferation and migration in HCC cell lines by decreasing the concentration of intracellular cAMP levels. Cimetidine may be a candidate chemopreventive agent for HCC. PMID: 17295779

Cimetidine as an adjuvant treatment in colorectal cancer. A double-blind, randomized pilot study.
Dis Colon Rectum. 1995 May;38(5):514-8.
Svendsen LB, Ross C, Knigge U, Frederiksen HJ, Graversen P, Kjaergård J, Luke M, Stimpel H, Sparsø BH.

PURPOSE: To evaluate the influence of a H2 receptor antagonist (cimetidine) on survival in patients with colorectal carcinoma, a randomized, controlled pilot study was performed in three university hospitals in Copenhagen, Denmark. METHODS: A total of 192 patients, who had undergone a resection or an exploratory operation for adenocarcinoma of the colon or rectum between May 1988 and May 1991, were enrolled in the study. After a median observation time of 40 months, outcome was noted for each patient concerning cancer-specific mortality rate. RESULTS: In patients operated with curative intent (n = 148), no difference was found in cancer-specific mortality between the two treatments. However, a tendency toward reduction in mortality rate was found in patients with curatively operated Dukes Stage C carcinoma (P = 0.11, log-rank test; difference, 29 percent; 90 percent confidence interval, 2 to 57 percent) in the cimetidine-treated group. In patients with disseminated disease no total difference was found between the two treatment groups. CONCLUSIONS: Cimetidine does not seem to reduce mortality in patients with colorectal cancer, but there seems to be a tendency toward a survival benefit in patients undergoing surgery for Dukes Stage C carcinoma. Results seem to justify trials in this patient category to reveal a benefit of H2 receptor antagonists in adjuvant therapy of colorectal carcinoma. PMID: 7736883

Cimetidine, an unexpected anti-tumor agent, and its potential for the treatment of glioblastoma (review). Int J Oncol. 2006 May;28(5):1021-30.
Lefranc F, Yeaton P, Brotchi J, Kiss R.
Cimetidine (CIM), the prototypical histamine H2 receptor antagonist (H2RA), was brought to market based on its ability to accelerate healing of gastrointestinal ulcers through the inhibition of gastric acid secretion. Cimetidine, the most studied H2RA, has been demonstrated to possess anti-tumor activity against colon, gastric and kidney cancers, and melanomas. This activity involves a number of different mechanisms of action: a) CIM antagonizes tumor cell-mediated interleukin-1-induced activation of selectins in liver sinusoids, inhibiting tumor cell binding on liver sinusoids, thereby reducing the development of liver metastasis; b) histamine acts as a growth factor in various tumor cell types via the activation of H2 receptors; CIM therefore may antagonize this effect; c) CIM acts as an immunomodulator by enhancing the host's immune response to tumor cells. With respect to malignant gliomas, CIM added to temozolomide was superior in vivo when compared to temozolomide alone in extending survival of nude mice with human glioblastoma cells orthotopically xenografted into their brain. We review the various mechanisms of action potentially associated with the therapeutic effects of CIM in the case of experimental glioblastomas, observations we hope will encourage clinical investigation of CIM in the management of highly malignant gliomas. PMID: 16596218

Cimetidine induces apoptosis of human salivary gland tumor cells Oncol Rep. 2007 Mar;17(3):673-8. Fukuda M, Tanaka S, Suzuki S, Kusama K, Kaneko T, Sakashita H.
It has been reported that cimetidine, a histamine type-2 receptor (H2R) antagonist, inhibits the growth of glandular tumors such as colorectal cancer. However, its effects against salivary gland tumors are still unknown. We demonstrated previously that human salivary gland tumor (HSG) cells spontaneously express the neural cell adhesion molecule (NCAM) and also that HSG cell proliferation could be controlled via a homophilic (NCAM-NCAM) binding mechanism and that NCAM may be associated with perineural invasion by malignant salivary gland tumors. In the present study, we investigated the effects of cimetidine via the expression of NCAM on tumor growth and perineural/neural invasion in salivary gland tumor cells. Expression of both NCAM mRNA and protein was found to decrease in a dose-dependent manner upon treatment with cimetidine for 24 h. The MTT assay and confocal laser microscopy clearly showed that HSG cells underwent apoptosis after treatment with cimetidine. Activation of caspases 3, 7, 8 and 9 was observed in HSG cells after cimetidine treatment, thus confirming that the apoptosis was induced by the activated caspases. Apaf-1 activity was also detected in HSG cells in a dose-dependent manner after treatment with cimetidine. We also found that the cimetidine-mediated down-regulation of NCAM expression in HSG cells did not occur via blocking of the histamine receptor, even though H2R expression was observed on HSG cells, as two other H2R antagonists, famotidine and ranitidine, did not show similar effects. We demonstrated for the first time that cimetidine can induce significant apoptosis of salivary gland tumor cells, which express NCAM, at least in part by down-regulation of NCAM expression on the cells. These findings suggest that the growth, development and perineural/neural invasion of salivary gland tumor cells can be blocked by cimetidine administration through down-regulation of NCAM expression, as well as induction of apoptosis.PMID: 17273750

Cimetidine use and the risk for prostate cancer: results from the VITAL cohort

study Ann Epidemiol. 2006 Dec;16(12):895-900. Epub 2006 Jul 12.
Velicer CM, Dublin S, White E.
PURPOSE: The histamine-2 (H(2)) blocker cimetidine may alter androgen, zinc, and prolactin levels, which could alter prostate cancer risk. Increased risk for men filling more than 20 cimetidine prescriptions was reported previously. We examined the association between cimetidine use and prostate cancer risk in a cohort in western Washington State. METHODS: Participants were 33,506 men, 50 to 76 years old, enrolled in the VITamins And Lifestyle cohort (VITAL). H(2)-blocker use during the prior 10 years was self-reported through baseline questionnaire between October 2000 and December 2002. Men were followed up for subsequent prostate cancer by linkage to the Surveillance, Epidemiology and End Results cancer registry. We identified 548 incident invasive prostate cancer cases diagnosed from baseline to December 31, 2003. RESULTS: Overall, no association between ever use of cimetidine or years of cimetidine use and prostate cancer risk was observed. However, daily cimetidine use for 10 years was associated with increased risk (relative risk, 2.35; 95% confidence interval, 1.05-5.26) compared with nonuse of any H(2) blockers. Use of other H(2) blockers was not associated with prostate cancer. CONCLUSIONS: Additional studies are needed to determine whether long-term daily cimetidine use is associated with increased prostate cancer risk in other populations, and if so, the reason for this association. MID: 16843010

Cimetidine use and risk of prostate and breast cancer. Cancer Epidemiol Biomarkers Prev. 2000 Mar;9(3):319-23 Rossing MA, Scholes D, Cushing-Haugen KL, Voigt LF.
Histamine (H2) receptor antagonists, such as cimetidine and ranitidine, became available in the late 1970s and presently number among the most commonly used drugs. Cimetidine has been hypothesized to exert a cancer preventive effect on the prostate due to its ability to inhibit the binding of dihydrotestosterone to androgen receptors. Other hormonal effects of this drug include increases in serum prolactin levels and inhibition of 2-hydroxylation of estradiol. We assessed risk of prostate and breast cancers in a cohort of 48,512 members of the Group Health Cooperative of Puget Sound prescribed cimetidine or another H2 blocker between 1977 and 1995. Standardized incidence ratios were calculated comparing the observed numbers of cancers to those expected based on population rates in western Washington State. Because cimetidine, but not other H2 blockers, influences hormonal activity and metabolism, we conducted nested case-control studies comparing cancer risk among individuals treated with cimetidine to individuals who used other H2 blockers. Risks of breast and prostate cancers were identical among users of cimetidine and users of other H2 blockers (relative risk, 1.0 for both cancers). We observed no trend in risk of breast cancer according to time since first or last cimetidine prescription or number of cimetidine prescriptions filled. For prostate cancer, our findings were similar save for a modest increase in risk among men who had filled > or =21 cimetidine prescriptions (relative risk, 1.4; 95% confidence interval, 1.0-1.9). Our results suggest that use of cimetidine does not influence risk of female breast cancer. Further, these data provide little evidence to support the previously hypothesized preventive effect of cimetidine on risk of prostate cancer.PMID: 10750671

Histamine regulates growth of malignant melanoma implants via H2 receptors in mice. Inflammopharmacology. 2005;13(1-3):281-9
Tomita K, Nakamura E, Okabe S.

The present study examined the effect of histamine H2-receptor antagonists and exogenous histamine on growth of malignant melanoma implant in mice. Drugs were administered to B16BL6 malignant-melanoma-implanted syngeneic mice, and the tumor volume was measured throughout the experiments. Cell proliferation was assessed by MTT assay and mRNA expression was determined by RT-PCR. Both roxatidine and cimetidine significantly suppressed growth of B16BL6 implant compared with vehicle. On the other hand, systemically administered histamine significantly stimulated growth of B16BL6 implants. In addition, the histamine-stimulated B16BL6 implant growth was markedly suppressed by co-administration of cimetidine in a dose-dependent manner. H2-receptor antagonists, however, failed to affect in vitro proliferation of B16BL6 cells. H2-receptor mRNA was detected in B16BL6 implants but not in the cell line. These results indicated that both endogenous and exogenous histamine have ability to stimulate growth of malignant melanoma implants via H2 receptors expressed in host cells.PMID: 16259747

Cimetidine inhibits cancer cell adhesion to endothelial cells and prevents metastasis by blocking E-selectin expression. Cancer Res. 2000 Jul 15;60(14):3978-84.
Kobayashi K, Matsumoto S, Morishima T, Kawabe T, Okamoto T.
Although the beneficial effect of cimetidine on survival in cancer has been clinically demonstrated in colorectal cancer patients, the mode of action of cimetidine has not been elucidated. In this report, we have demonstrated for the first time that cimetidine can block the adhesion of a colorectal tumor 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. We also demonstrated that these antimetastasis effects of cimetidine might occur through down-regulation of the cell surface expression of E-selectin on endothelial cells, a ligand for sialyl Lewis antigens on tumor cells. We found that the cimetidine-mediated down-regulation of E-selectin did not involve down-regulation of E-selectin mRNA or blocking of the nuclear translocation of nuclear factor kappaB, a transcriptional activator of E-selectin gene expression. Because two other histamine type 2 receptor antagonists, famotidine and ranitidine, did not show any similar effect, these actions of cimetidine probably do not occur via blocking of the histamine receptor. These observations support the idea that cancer metastasis can be blocked by cimetidine administration through blocking the adhesion of tumor cells to the endothelium when an interaction between E-selectin and sialyl-Lewis antigens plays a role.PMID: 10919677

Cimetidine induces interleukin-18 production through H2-agonist activity in monocytes Mol Pharmacol. 2006 Aug;70(2):450-3. Epub 2006 May 24
Takahashi HK, Watanabe T, Yokoyama A, Iwagaki H, Yoshino T, Tanaka N, Nishibori M.
The present study demonstrates a possible mechanism for the improvement of gastrointestinal cancer patients' prognosis by the histamine receptor type 2 (H2R) antagonist cimetidine. This agent, but not the H2R antagonists ranitidine and famotidine, induced the production of an antitumor cytokine, interleukin (IL)-18, by human monocytes and dendritic cells (DC). In fact, ranitidine and famotidine antagonized cimetidine-induced IL-18 production. Cimetidine induced the activation of caspase-1, which is reported to modify immature IL-18 to mature/active IL-18, and the elevation of intracellular cAMP, leading to the activation of protein kinase A (PKA). The PKA inhibitor H89 abolished the IL-18 production induced by cimetidine. Moreover, the effects of cimetidine on IL-18 production were reproduced in peripheral blood mononuclear cells from wild-type mice, but not in those from H2R knockout mice. In conclusion, cimetidine, a partial agonist for H2R, has a pharmacological profile different from ranitidine and famotidine, possibly contributing to its antitumor activity on gastrointestinal cancers.PMID: 16723495

Can the survival of patients with recurrent disease after curative resection of colorectal cancer improve with cimetidine Gan To Kagaku Ryoho. 2006 Nov;33(12):1730-2
Yoshimatsu K, Ishibashi K, Yokomizo H, Umehara A, Yoshida K, Fujimoto T, Watanabe K, Otani T, Matsumoto A, Osawa G, Ogawa K.
Administration of cimetidine after curative surgery can improve prognosis of patients with colorectal cancer. In this study, we analyzed whether cimetidine can influence the survival of patients with a recurrent disease after colorectal surgery. The subjects were 29 patients with recurrent disease: 14 patients were administered with cimetidine and 15 patients were not. In the cimetidine administered group, seven cases were recurrent in the liver, 5 cases in a local site and 1 case in the lymph node, whereas 7 cases were recurrent in the liver, 4 cases in a local site and 3 cases in the lung for the non-cimetidine administered group. There were no significant differences for both groups in terms of patient's survival after recurrence. Although it was not significant, the patient's survival after curative resection of recurrent disease for the cimetidine administered group was better than the non cimetidine administered group. Although the results did not show cimetidine could influence the overall survival of the patients after recurrence, it might be possible to improve the survival of

the patients after resection of the recurrent disease.

Outras Referências Bibliográficas de grande valor

1. Adams W. J., Morris D. L. Short-course cimetidine and survival with colorectal cancer. Lancet, *344:* 1768-1769, 1994.
2. Matsumoto S. Cimetidine and survival with colorectal cancer. Lancet, *346:* 115 1995.
3. Svendsen L. B., Ross C., Knigge U., Frederiksen H. J., Graversen P., Kjaergard J., Luke M., Stimpel H., Sparso B. H. Cimetidine as an adjuvant treatment in colorectal cancer. Dis. Colon Rectum, *38:* 514-518, 1995.
4. Hellstrand K., Naredi P., Lindner P., Lundholm K., Rudenstam C. M., Hermodsson S., Asztely M., Hafstrom L. Histamine in immunotherapy of advanced melanoma. Cancer Immunol. Immunother, *39:* 416-419, 1994.
5. Creagan E. T., Ahman D. L., Green S. J., Long H. J., Frytak S., Itri L. M. Phase II study of recombinant leukocyte A interferon (IFN-RA) plus cimetidine in disseminated malignant melanoma. J. Clin. Oncol, *3:* 977-981, 1992.
6. Sagaster P., Micksche M., Flamm J., Ludwig H. Randomised study using IFN-{alpha} *versus* IFN-{alpha} plus coumarin and cimetidine for treatment of advanced renal cell cancer. Ann. Oncol, *6:* 999-1003, 1995.
7. Morris D. L., Adams W. J. Cimetidine and colorectal cancer—old drug, new use?. Nat. Med, *1:* 1243-1244, 1995.
8. Kelly M. D., King J., Cherian M., Dwerryhouse S. J., Finlay I. G., Adams W. J., King D. W., Lubowski D. Z., Morris D. L. Randomized trial of preoperative cimetidine in patients with colorectal carcinoma with quantitative assessment of tumor-associated lymphocytes. Cancer (Phila.), *85:* 1658-1663, 1999.[Medline]
9. Sasson A. R., Gamagami R., An Z., Wang X., Moossa A. R., Hoffman R. M. Cimetidine: an inhibitor or promoter of tumor growth?. Int. J. Cancer, *81:* 835-838, 1999.
10. Hansbrough J. F., Zapata-Sirvent R. L., Bender E. M. Prevention of alterations in postoperative lymphocyte subpopulations by cimetidine and ibuprofen. Am. J. Surg, *151:* 249-255, 1986.
11. Adams W. J., Lawson J. A., Morris D. L. Cimetidine inhibits *in vivo* growth of human colon cancer and reverses histamine stimulated *in vitro* and *in vivo* growth. Gut, *35:* 1632-1636, 1994