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COVER STORY

Cimetidine (Tagamet®)
For Cancer Treatment

Cimetidine (brand name Tagamet®) is a drug historically used to reduce stomach acid production. Published research dating back more than 20 years shows that this drug might make a greater impact in medicine if used as a cancer therapy rather than as a treatment for gastric disorders.

Since cimetidine is so well known as an H2 blocker medication to reduce stomach acid secretion, its role in cancer treatment has been grossly overlooked. This same misperception occurred when aspirin was first recommended to prevent a heart attack or stroke. Doctors were accustomed to prescribing aspirin to relieve pain and inflammation, but were unfamiliar with the concept of taking aspirin to prevent cardiovascular disease and thrombotic events.



It is now the standard of care for a patient who has had a heart attack or stroke to be placed on aspirin as long as there are no individual contraindications. To date, the proven benefits of cimetidine to treat cancer have not been recognized by the medical community. The results of a brand new study on colon cancer patients may provide enough compelling evidence to convince oncologists that cimetidine is an effective adjuvant therapy.

In this article, we discuss research that substantiates the anti-cancer benefits of cimetidine and reveal what types of colon cancer cimetidine has been shown to be effective against. The brand name for cimetidine is Tagamet®, which is sold over-the-counter and as a prescription medication.

The first studies suggesting that cimetidine (Tagamet®) might be effective against cancer were published in the late 1970s. Scientists initially thought that cimetidine worked by enhancing immune function. Later studies showed that cimetidine functions via several different pathways to inhibit tumor cell propagation and metastasis.

In 1988 a prospective, randomized, placebo controlled study investigated the effect of cimetidine on the survival of 181 patients with gastric cancer. They were given either cimetidine at a dose of 400 mg twice daily or placebo for two years or until death. The study found that those given cimetidine had a significantly prolonged survival rate particularly in patients with more serious (stage II and IV) disease.[1] This finding is especially notable in light of what we know today about the mechanism of action of cimetidine.

In 1994, a study was performed that demonstrated that just seven days of treatment with cimetidine (five days pre-operative and two days post-operative) decreased the three-year mortality rate from 41% to 7% in colorectal cancer patients. Another observation was that the tumors from the treated patients had a significantly higher rate of infiltration by lymphocytes.[2] These tumor infiltrating lymphocytes (TIL) are a good prognostic indicator because they are part of the body's immune response to the tumor. With more TIL present, the body is more capable of attacking and eliminating the tumor. These observations led the scientific community to hypothesize that cimetidine functioned by augmenting the immune response to cancer in some fashion.

The latest study published in the British Journal of Cancer, January, 2002, was conducted through the collaboration of 15 institutions in Japan. After surgery to remove the primary tumor followed by IV Mitomycin chemotherapy, all patients were given either 200 mg of oral 5-FU or 200 mg of 5-FU with 800 mg of oral cimetidine daily for 12 consecutive months. The patients were followed for 10 years. The study showed a more than three-fold improvement in 10-year survival of Dukes C colon cancer patients who were given cimetidine. Interestingly, the less aggressive forms of colon cancer (Duke A or B) did not respond as remarkably to the addition of cimetidine in this study as the more aggressive Dukes C.[3]

How cimetidine works



by Dr. Michele Morrow, Board Certified Family Physician & Life Extension Medical Advisor

Cimetidine is a competitive inhibitor of the histamine receptors on the cells of the stomach that secrete acid. It binds to these receptors, called H2 receptors, and doesn't allow histamine to bind. Histamine is responsible for signaling these cells to secrete acid. If cimetidine is present, the cells don't get the signal to produce acid thus reducing the pH of the stomach.

Cimetidine has been in use to treat gastric disorders since 1975. Prior to the advent of stronger anti-emetics, this drug was also prescribed to treat the nausea associated with chemotherapy. In 1988 it was observed that colon cancer patients who had been treated with cimetidine had a significantly better response than those who had not received the drug. Many hypotheses were offered to explain this phenomenon. Since cimetidine is a histamine receptor antagonist, it was suggested that the actions were mediated by this mechanism.

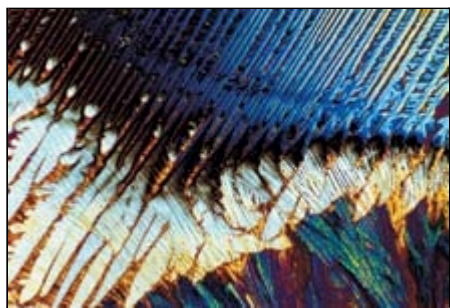
Histamine is also one of the compounds the body secretes to inhibit an immune response. Histamine can be released in the tumor environment and act to suppress the immune response that the body may mount to attack a tumor. If cimetidine inhibited this suppression, then the immune system may be able to build up a more effective response to the tumor and the cancer could be attacked by the immune system. This may be one of the mechanisms through which cimetidine works, however, other H2-blockers (ranitidine for example) that are stronger than cimetidine do not demonstrate this effect to the same degree as cimetidine.

It was postulated that cimetidine may exert an effect on the ability of cancer cells to metastasize. Indeed, it was recently found that cimetidine does inhibit the ability of cancer cells to attach to vascular endothelium. It was then discovered that cimetidine inhibits the expression of E-selectin (ELAM-1) which is one of the molecules in blood vessels that cancer cells adhere to using their own cell surface ligands, Lewis X and Lewis A.⁴ These are carbohydrate groups on the surface on certain cancer cells that allow them to bind to E-selectin.

Since cimetidine inhibits the expression of E-selectin in blood vessels, cancer cells that are in the bloodstream can't bind to the blood vessels and establish a metastatic tumor. Instead they are eventually eliminated. This would obviously lead to a much better outcome for the patient. Indeed, patients with aggressive colon cancer (Dukes grade C) had a remarkable 84.6% ten year survival rate when treated with cimetidine for one year after surgery compared to a 23.1% ten year survival rate for patients that were not treated with cimetidine as an adjuvant therapy.^[3]

Cimetidine as an immunomodulator

While it has been observed that histamine is a growth factor for certain cancers and can, by itself, stimulate these cells to proliferate^[5], it does not seem that the inhibition of this histamine action that cimetidine causes is primarily responsible for its efficacy.^[6] There are, however, many indications that cimetidine has an effect on the immune system and the ability of the body to respond to a tumor.



In 1972, it was discovered that T suppressor cells, which are part of the regulatory arm of the immune system, express receptors for histamine on their surface.^[7] T suppressor cells have been demonstrated to accelerate the growth of tumors. It was also demonstrated that histamine was capable of suppressing the immune response by activating these T suppressor cells.^[8] Many tumors, particularly colorectal cancers, secrete histamine resulting in elevated histamine levels within the tumor. Histamine is also often secreted in response to surgical resection of colorectal cancers and significant immunosuppression ensues from this and other factors.

Several studies have shown that administration of H2 antagonists inhibit this immune

How Colon Cancer Patients Can Determine If Cimetidine Will Be Effective For Them

Colon cancer patients should ask that their tumor specimen be sent to a laboratory to determine the Lewis antigen expression of the cancer cells.

Lewis X and Lewis A antigens are cell surface ligands on cancer cells that adhere to a molecule found in blood vessels called E-selectin. The adhering of cancer cells to E-selectin on a blood vessel wall initiates the metastatic process.

In one study, approximately 70% of colon cancers examined expressed high levels of these Lewis antigens.* Other cancers such as breast and pancreatic have been demonstrated to express these Lewis antigens also.

Since cimetidine inhibits the expression of E-selectin in blood vessels, cancer cells in the bloodstream that express Lewis X or Lewis A antigens can't bind to the blood vessels and establish a metastatic tumor. These cells are instead eventually eliminated.

In order to determine the Lewis antigen expression of your cancer cells, contact:

IMPATh Laboratories
521 West 57th Street
New York, NY 10019
Phone: 1-800-447-5816

* Matsumoto S, Imaeda Y, Umemoto S, Kobayashi K, Suzuki H, Okamoto T. Cimetidine increases survival of colorectal cancer patients with high levels of sialyl Lewis-X and sialyl Lewis-A epitope expression on tumour cells. *Brit J Can* 2002 (86) 161-167.

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Pictured: molecular expression of cimetidine.

suppressive function of histamine.[13] In addition to the presence of TIL, the ability of peripheral lymphocytes to kill tumor cells is associated with enhanced disease free survival.[14] Post-operative administration of cimetidine may enhance the function of these cells as well.

Cimetidine interferes with metastasis

Adhesion molecules are expressed on the surface of many different cell types to facilitate their adhering to other cells. These molecules play a critical role in many different biological processes including wound healing, the immune response and cancer metastasis.

Cells circulating in the blood must have a mechanism by which they can stop circulating, bind to the cells in the area of interest and perform their various functions. For a lymphocyte, this means that it has the ability to travel to a site of infection or a wound and stop there to perform its immunological functions. Similarly, for a cancer cell to bind and proliferate in an area, it must first adhere to the inside of a blood vessel. One of these adhesion molecules that are present on blood vessels is called E-selectin. Several types of cancer cells use carbohydrate moieties called Lewis antigens to bind to E-selectin. It was recently discovered that cimetidine can block the expression of E-selectin and inhibit cancer cell adhesion in vitro and can inhibit the metastasis of liver cancer in a nude mouse model. This mechanism of action seems to be independent of the ability of cimetidine to block the H2 receptor.[4]

After this discovery was made, one researcher went back to look at the Lewis antigen expression in tumors which were resected from patients that had been treated with cimetidine. From 1990 to 1992, 64 patients were enrolled in a study to examine the effects of cimetidine. Patients were treated for one year after surgery with 5-fluorouracil and cimetidine or 5-fluorouracil alone. In a recently published summary of that study, the results are truly remarkable. Overall, the 10-year survival rate for the cimetidine treated group was 84.6%. The group 10-year survival rate of the group that received 5-fluorouracil alone was 49.8%. When the tumors were analyzed for Lewis antigen expression, those patients who had tumors with the Lewis antigen and were treated with cimetidine had an average survival rate of 90.7% compared to 33.7% for those that were not treated with cimetidine. For those patients whose tumors did not express the Lewis antigens, there was no significant difference between cimetidine treated and untreated. However, approximately 70% of the tumors in this study did express the Lewis antigen.[3]

Conclusion

The beneficial effects of cimetidine in the treatment of colon cancer are well documented. These effects probably arise from the multiple actions of cimetidine as an H2 receptor antagonist, an immunomodulator and as an inhibitor of adhesion molecule expression, but it is not yet approved by the FDA for use in these diseases. Since cimetidine's effect was not studied without the inclusion of another drug (5-FU), it is unclear if the effect is additive or synergistic. The proven mechanisms of action of cimetidine suggest that alone it would significantly alter the ability of certain colon cancers to grow and metastasize, however, further studies should be done to evaluate and document the efficacy of cimetidine on its own.

Clearly, cimetidine has a place in the treatment of colorectal cancer whether it be on its own or as an adjuvant medication. In 2001, there were 135,000 cases of newly diagnosed cancer of the colon and rectum and 56,700 deaths from these cancers.[15] If these patients had the knowledge to take 800 mg each night of cimetidine, many of them might still be alive today.

Note: Tagamet® is no longer the drug of choice for gastric ulceration or esophageal reflux (heartburn). Esophageal reflux is better treated with a class of drugs called proton pump inhibitors that completely block stomach acid production (ie: Prolisec®, Prevacid®, Nexium®) while most stomach ulcers can be healed with antibiotic therapy that kills the H-pylori bacteria.

Note: If you wish to take cimetidine you should notify your physician. The drug interacts with several other medications to either

suppression.[9-11] During surgery, some cancer cells may be released into the blood stream and a suppressed immune system may contribute to their ability to escape immune surveillance and establish metastatic lesions. If the immune system is suppressed, these cells stand a better chance of becoming tumors.

In addition, many tumors are infiltrated with lymphocytes as a part of the immune response. These tumor infiltrating lymphocytes (TIL) are associated with a better prognosis than tumors lacking in TIL.[12] Administration of cimetidine significantly elevated the proportion of colorectal cancers with TIL, probably by inhibiting the



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increase or decrease their potency. Some of these medications include digoxin, theophylline, phenytoin, warfarin and lidocaine.

References

1. Tonnesen H, Knigge U, Bulow S, Damm P, Fischerman K, Hesselfeldt P, Hjortrup A, Pedersen IK, Pedersen VM, Siemssen OJ. Effect of cimetidine on survival after gastric cancer. *Lancet* 1988 Oct 29;2(8618):990-2.
2. Adams WJ, Morris DL. Short-course cimetidine and survival with colorectal cancer. *Lancet*. 1994 Dec 24-31;344(8939-8940):1768-9.
3. Matsumoto S, Imaeda Y, Umemoto S, Kobayashi K, Suzuki H, Okamoto T. Cimetidine increases survival of colorectal cancer patients with high levels of sialyl Lewis-X and sialyl Lewis-A epitope expression on tumour cells. *Brit J Can* 2002 (86) 161-167.
4. Kobayashi K, Matsumoto S, Morishima T, Kawabe T, Okamoto T. 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.
5. Adams WJ, Lawson JA, Morris DL. Cimetidine inhibits in vivo growth of human colon cancer and reverses histamine stimulated in vitro and in vivo growth. *Gut* 1994 Nov;35(11):1632-6.
6. Siegers CP, Hiltl DM, Stich R. Cimetidine hemmt das Tumorzellwachstum. *Therapie-woche*. 1995 (36) 2110-2114.
7. Melmon KL, Bourne HR, Weinstein Y, Sela MD. Receptors for histamine can be detected on the surface of selected leukocytes. *Science* 1972 (177) 707.
8. Rocklin RE, Greineder DK, Melmon KL. Histamine induced suppressor factor (HSF) Further studies on the nature of the stimulus and the cell which produces it. *Cell Immunol* 1979 (44) 404-415.
9. Hansbrough J, Zapata-Sirvent R, Bender E. Prevention of alterations in postoperative lymphocyte subpopulations by cimetidine and ibuprofen. *Am. J surg* 1986 151, 249-255.
10. Adams W. Cimetidine preserves immune function after colonic resection of cancer. *Aust. NZ J. Surg* 1994 64, 847-852.
11. Adams WJ, Lawson JA, Nicholson SE, Cook TA, Morris DL. The growth of carcinogen-induced colon cancer in rats is inhibited by cimetidine. *Eur J Surg Oncol* 1993 Aug;19 (4):332-5.
12. Harrison JC, Dean PJ, El-Zeky F, Vander Zwaag R. From Dukes through Jass: Pathological prognostic indicators in rectal cancer. *Hum. Path.* 1994 (25) 495-498.
13. Morris DL, Adams WJ. Cimetidine and colorectal cancer-old drug, new use? *Nat Med*. 1995 Dec;1(12):1243-4.
14. Uchida A. Biological significance of autologous tumour killing activity and its induction therapy. *Cancer Immun. Immunother* 1993 (37) 75-83.
15. American Cancer Society website - Statistics section.

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