

LE Magazine May 2007

## REPORT

### Cimetidine

#### A Common Heartburn Remedy Complements Conventional Cancer Therapy

By Cynthia Haines, MD



Conventional cancer therapies do not always eradicate the cancer, leading patients to seek out adjuvant therapies that may confer additional benefits.

More than two decades ago, Life Extension called attention to the over-the-counter heartburn drug cimetidine—more commonly known by its brand name, Tagamet®—as a complementary cancer treatment. Although cimetidine was developed to relieve heartburn, acid indigestion, and sour stomach, numerous studies demonstrate that this readily available medication may offer powerful support in the fight against cancer. Unfortunately, many cancer patients and even oncologists remain unaware of the compelling evidence demonstrating its efficacy.

By preventing cancer metastasis (spread), slowing or halting tumor growth, and prolonging survival, cimetidine may serve as an important adjuvant therapy for people fighting colon cancer and other

malignancies.

#### WHAT IS CIMETIDINE?

Cimetidine, or Tagamet®, reduces the production of stomach acid by binding with H2 receptors on the acid-secreting cells of the stomach lining. These receptors normally bind with histamine to produce stomach acid, which helps to break down food. By competing with histamine to bind with H2 receptors, cimetidine reduces the stomach's production of acid.

This mechanism of action accounts for cimetidine's use in managing gastroesophageal reflux disease (GERD), a condition marked by an excess of stomach acid. In fact, its use in treating gastric (stomach) disorders dates back several decades.

Anti-emetic drugs are used to prevent or treat nausea and vomiting. Before stronger anti-emetic drugs became available, cimetidine was prescribed to treat nausea associated with chemotherapy. As far back as 1988, scientists observed that colon cancer patients who had been treated with cimetidine had a notably better response to cancer therapy than those who did not receive cimetidine.<sup>1</sup> Now, nearly 30 years of published research suggests that cimetidine may exert its most profound effects not as a heartburn remedy, but as an anti-cancer drug.

#### AN UNEXPECTED ANTI-CANCER AGENT

The first studies to hint at cimetidine's effectiveness against cancer were published in the late 1970s. Although scientists initially thought that cimetidine worked by enhancing immune function, later studies showed that cimetidine functions via several different pathways to inhibit tumor cell proliferation and metastasis

In a prospective, randomized, placebo-controlled study in 1988, 181 patients with gastric cancer received cimetidine (400 mg, twice daily) or placebo for two years or until death. Those given cimetidine had a significantly prolonged survival rate compared to the placebo group, particularly patients with more serious disease.<sup>1</sup>

In a 1994 study, just seven days of cimetidine treatment (400 mg twice daily for five days preoperative and intravenously for two days post-operative) in colorectal cancer patients decreased their three-year mortality rate from 41% to 7%. In addition, tumors in the cimetidine-treated patients had a notably higher rate of infiltration by lymphocytes, a type of white blood cell.<sup>2</sup> These tumor-infiltrating lymphocytes, part of the body's immune response to the tumor, serve as a good prognostic indicator. When more tumor-infiltrating lymphocytes are present, the body is more capable of attack-ing and eliminating the tumor.



A report in the British Journal of Cancer examined findings of a collaborative colon cancer study conducted by 15 institutions in Japan. First, all participants had surgery to remove the primary colorectal tumor, followed by intravenous chemotherapy treatment. They were then divided into two groups: one group received 800 mg of oral cimetidine and 200 mg of fluorouracil (a cancer-fighting medication) daily for one year, while a control group received fluorouracil only. The patients were followed for 10 years. Cimetidine greatly improved the 10-year survival rate: 85% of the cimetidine-treated patients survived 10 years, while only 50% of the control group survived.<sup>3</sup> Cimetidine produced the greatest survival-enhancing benefits in those whose cancer cells showed markers associated with the tendency to metastasize.

In just the last two years, several other studies have corroborated cimetidine's benefits for surviving colorectal cancer. For instance, in a Japanese study in 2006, colorectal cancer patients who received cimetidine following surgical removal of recurrent cancer had an improved prognosis compared to those treated with surgery only.<sup>4</sup>

A groundbreaking study reported in the International Journal of Oncology in 2006 confirms decades of research highlighting cimetidine's role as an important adjuvant cancer therapy. This study demonstrated that cimetidine may enhance survival in those undergoing conventional treatment for brain tumors.<sup>5</sup> The most common primary brain tumors in adults and children, known as malignant gliomas (tumors that begin in the supportive cells of the brain or spinal cord), often fail to respond to chemotherapy, and are frequently fatal. Mice with tissue grafts of human glioblastoma cells that received both cimetidine and the chemotherapy drug temozolomide (Temodar®) demonstrated improved survival rates compared to those that received chemotherapy only. Cimetidine may thus prolong survival in people undergoing chemotherapy for the most prevalent type of brain tumor.

## HOW DOES CIMETIDINE FIGHT CANCER?

Since cimetidine's anti-cancer effects were first reported, scientists have proposed several hypotheses to explain how the drug works. Cimetidine's potential mechanisms of action include:

- modulating the body's immune response (immunomodulation)
- interfering with tumor growth
- inhibiting tumor cell migration and metastasis.

## CIMETIDINE MODULATES THE IMMUNE SYSTEM

Histamine plays many roles in the body—contributing to allergic responses, regulating physiological function in the gut, and acting as a neurotransmitter. Histamine secretion also has the effect of suppressing the immune system.

Many cancers, particularly colorectal and breast tumors, secrete histamine.<sup>3,5,6</sup> Histamine secretion also frequently occurs in response to surgical resection of colorectal cancers.<sup>6</sup> In the tumor environment, histamine acts to suppress the immune response the body mounts to attack a tumor. This creates an immunosuppressive environment in the area of tumor growth and throughout the body, thus facilitating tumor growth.

Since cimetidine is a histamine receptor antagonist—that is, an agent that binds with a cell receptor without eliciting a biological response—it may help reduce immunosuppression caused by increased histamine levels in a tumor's environment.<sup>6,7</sup> Administering cimetidine may enable the immune system to mount a more effective response, so that it can attack and potentially eliminate the tumor.

While histamine appears to stimulate the growth and proliferation of certain types of cancer cells,<sup>8</sup> inhibiting histamine's action may be only one mechanism by which cimetidine fights cancer.<sup>9</sup> Researchers have found evidence that cimetidine has many different effects on the immune system and the body's ability to respond to a tumor.

In 1972, for example, scientists discovered that T-suppressor cells in the immune system express receptors for histamine on their surface.<sup>10,11</sup> T-suppressor cells accelerate the growth of tumors,<sup>12</sup> and by activating these cells, histamine suppresses the immune response.<sup>13</sup> Several studies have shown that cimetidine inhibits this immune suppression and helps restore a normal immune response.<sup>7,14-16</sup> Compared to normal controls, gastric cancer patients also have higher levels of suppressor lymphocyte activity, and cimetidine treatment helps restore these levels to normal.<sup>17</sup>

During surgery, some cancer cells may be released into the bloodstream. A suppressed immune system may contribute to the ability of these residual cancer cells to escape immune surveillance and establish metastatic lesions.<sup>7,15,16</sup> Cimetidine's ability to reverse immune suppression could thus help the immune system to remain alert to challenges such as spreading cancer cells.

In addition, many tumors are infiltrated with lymphocytes as a part of the body's immune response. The presence of tumor-infiltrating lymphocytes in a tumor indicates a better prognosis than for tumors that lack these white blood cells.<sup>2,17</sup> With more tumor-infiltrating lymphocytes present, the body is more capable of attacking and eliminating the tumor. Administering cimetidine greatly elevated the proportion of colorectal cancers with tumor-infiltrating lymphocytes, probably by inhibiting the immunosuppressive function of histamine.<sup>18</sup>

Post-operative administration of cimetidine may also enhance the ability of cells known as peripheral lymphocytes to kill tumor cells, which is associated with enhanced disease-free survival.<sup>19</sup> The presence of a lymphocyte response has been correlated with improved cancer survival.<sup>20</sup> In a recent clinical study, cimetidine boosted peripheral blood lymphocytes and the tumor-infiltrating lymphocyte response. The authors concluded that administering cimetidine to gastrointestinal cancer patients several days before and after surgery may restore the diminished immune response often seen with cancer.<sup>21</sup>



A study from 2005 suggests cimetidine helps increase specific types of T-lymphocytes with protective attributes in the peripheral blood. Six healthy adults were given an 800-mg oral dose of cimetidine daily, and blood samples were collected at the study's onset and one, three, five, and seven days later. Cimetidine treatment was associated with an increase in white blood cells, specifically neutrophils (cells that fight bacterial invaders) and T-lymphocytes (which are involved in cell-mediated immunity). These results further suggest that cimetidine modulates cellular immunity and may be useful as an activator of tumor-specific immune response.<sup>22</sup>

In sum, cimetidine appears to support cellular immunity via several mechanisms, including blocking the immunosuppressive effect of histamine, inhibiting suppressor T-cell activity, increasing the number of tumor-infiltrating lymphocytes, and boosting the activity of peripheral blood lymphocytes.

## CIMETIDINE: WHAT YOU NEED TO KNOW

- Cimetidine is an over-the-counter, acid-blocking drug originally developed to treat heartburn, upset stomach, ulcers, and gastroesophageal reflux disease.
- In the 1980s, scientists noted that cancer patients who received cimetidine to manage chemotherapy-associated nausea experienced better outcomes, which led them to further investigate cimetidine's cancer-fighting effects.
- In 1985, Life Extension first called attention to cimetidine's promise as a novel anti-cancer therapy. Since then, more than 20 years of research has documented cimetidine's cancer-fighting effects.
- Used in conjunction with other cancer therapies, cimetidine has been found to significantly enhance cancer survival rates. Cimetidine works through several mechanisms of action, preventing immune suppression caused by tumor secretion of histamine, halting cancer growth, preventing angiogenesis, promoting cancer cell death, and averting often-fatal cancer metastasis.
- Further studies are needed to assess cimetidine's cancer-fighting abilities as both a sole therapeutic and an adjuvant cancer remedy.

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#### CIMETIDINE INHIBITS TUMOR GROWTH

In addition to its effects in boosting immunity, cimetidine may help to slow or halt cancer by inhibiting the growth of several types of tumors.<sup>8</sup>

For example, in a cell-culture study of four colorectal tumor cell lines and four melanoma cell lines, histamine stimulated cell proliferation in a dose-dependent manner, while cimetidine reversed this effect.<sup>8,23</sup> In another study, cimetidine inhibited the growth of human pancreatic cancer cells that had been grafted into immunodeficient mice.<sup>24</sup> These findings suggest possible applications for cimetidine in colorectal, skin, and pancreatic cancers.

Scientists believe that cimetidine may prolong the survival of patients with various forms of cancer by inhibiting tumor-associated angiogenesis,<sup>25,26</sup> the development of new blood vessels that tumors require to fuel their growth. In a 2005 report on cimetidine's effects on angiogenesis and tumor growth, cimetidine markedly reduced the growth (and production of new blood vessels needed to sustain the growth) of a grafted tumor in an animal model of colon cancer. These findings suggest that cimetidine suppresses tumor growth by inhibiting tumor-associated angiogenesis.<sup>25</sup>

Cimetidine may also fight cancer by promoting apoptosis (programmed cell death) in cancer cells. In a Chinese study from 2006, cimetidine induced apoptosis and halted cell division in human gastric cancer cells, leading the researchers to propose that cimetidine may have applications in treating gastric cancer.<sup>26</sup>

By shutting down the growth-stimulating effect of histamine, inhibiting angiogenesis, and promoting apoptosis, cimetidine thus appears to work via several mechanisms to arrest the growth of deadly tumors.

#### CIMETIDINE INHIBITS CANCER CELL METASTASIS

Most cancer deaths are caused not by primary tumors, but instead by metastases, or the secondary tumors that form when cells from the primary tumor spread to another location in the body. Cimetidine may prolong cancer survival by blocking the ability of cancer cells to metastasize to other locales in the body.

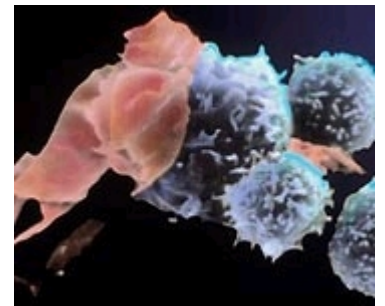
Adhesion molecules play a crucial role in many biological processes, such as wound healing, immune response, and cancer metastasis. These adhesion molecules are expressed on the surface of endothelial cells that line the blood vessels, which facilitates their adherence to other cells.

Adhesion molecules are intimately involved in the spread of cancer cells through the bloodstream to other locations where they will form secondary tumors. For example, when epithelial tumor cells enter blood vessels leading to the liver, they trigger the expression of an adhesion molecule called E-selectin in the liver blood vessel endothelium.<sup>27</sup> This helps cancer cells form a secondary tumor in the liver.

Several types of cancer cells use Lewis antigens—carbohydrate formations on cell surfaces that can activate an immune response—to bind with E-selectin in blood vessel walls. Cimetidine may help prevent cancer cells from migrating throughout the body and forming distant metastases by blocking the expression of E-selectin.

When given to immunosuppressed mice with liver cancer, cimetidine successfully blocked tumor metastasis. Cimetidine appears to be unique in its ability to block cancer metastasis—similar H2-blocking drugs such as famotidine (Pepcid®) and ranitidine (Zantac®) did not produce a similar effect.

Thus it appears that cimetidine's ability to block cancer metastasis is independent of its ability to bind the H2 histamine receptor.<sup>28</sup>



Upon discovering cimetidine's ability to block cancer metastasis, researchers re-visited a study in which colorectal cancer patients were treated with cimetidine immediately before and after cancer surgery. They found cimetidine was particularly effective in enhancing survival for colorectal cancer patients with tumors expressing higher levels of two Lewis antigens.<sup>3</sup> When the tumors were analyzed for Lewis antigen expression, patients who had tumors expressing Lewis antigens and who received cimetidine had a remarkable 10-year survival rate of 91%, compared to 34% for those not treated with cimetidine.

In 2003, Japanese researchers published findings indicating that cimetidine blocked the adhesion of gastric, esophageal, and breast cancer cells (all of which expressed a specific Lewis antigen) to epithelial cells expressing E-selectin. They concluded that cimetidine may be effective in preventing metastasis of these cancers.<sup>29</sup>

Cimetidine thus holds great promise in protecting against metastasis, the process that paves the way for cancer's often-fatal spread throughout the body.

## CONCLUSION

Cimetidine's beneficial effects in helping to manage various cancers are well documented. For more than 20 years, scientists have accumulated evidence that this low-cost, readily available heartburn remedy fights cancer via several mechanisms of action, including blocking the immunosuppressive action of histamine, modulating the body's immune response, inhibiting angiogenesis, stimulating cancer cell death, and inhibiting cancer metastasis.

Cimetidine has not yet been approved by the FDA for use in treating cancer, and it remains unclear how its effects may enhance or synergize with other cancer treatments. However, cimetidine's demonstrated effects suggest that it may markedly suppress the ability of certain cancers—particularly colorectal cancers—to grow and metastasize, even when used as a sole therapy. Further studies are needed to evaluate and document cimetidine's efficacy both alone and in concert with other cancer-fighting regimens.

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