Cimetidine: An anticancer drug?

Article *in* European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences · February 2011
DOI: 10.1016/j.ejps.2011.02.004 · Source: PubMed

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European Journal of Pharmaceutical Sciences 42 (2011) 439–444

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Review

Cimetidine: An anticancer drug?☆

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ARTICLE INFO

Article history:
Received 20 October 2010
Received in revised form
14 December 2010
Accepted 8 February 2011
Available online 15 February 2011

Keywords:
Cimetidine
H_2 blocker
Cancer
Tumor

ABSTRACT

Cimetidine, H_2 receptor antagonists, is commonly prescribed for gastric and duodenal ulcer disease. Additionally, cimetidine has been shown to have anticancer effects. This review describes the mechanism of antitumor action of cimetidine including its ability to interfere with tumor cell adhesion, angiogenesis and proliferation; its effect on the immune system; as well as inhibition of postoperative immunosuppression. Its anticancer effect is also compared to that of the other H_2 receptor antagonists as well as outcomes of cimetidine in clinical studies in cancer patients.

Contents

1. Introduction

Cimetidine is a substituted imidazole compound that functions as a histamine H_2-receptor antagonist, or H_2 blocker. H_2 blocker drugs are used to treat gastric and duodenal ulcers, gastroesophageal reflux disease, and as prophylaxis in conditions which produce high levels of gastric acidity. These drug, most commonly cimetidine, ranitidine, and famotidine, may also have an immunomodulatory effect by virtue of their interaction with H_2 receptors on cells in the immune system.

Some evidence suggests that these immunomodulating functions are the cause of the antitumor action of cimetidine. It was initially postulated that cimetidine works by enhancing immune function though more recent studies have shown that cimetidine functions via several different pathways such as anti-adhesion and antiangiogenesis, to inhibit tumor cell propagation and metastasis (Table 1).

2. Mechanisms of action

2.1. Cell proliferation and apoptosis

Histamine formed by L-histidine decarboxylase is involved in various physiological and pathophysiological processes, such as inflammation, allergy, gastric acid secretion and neurotransmission (Beaven, 1976; Code, 1965; Schwartz et al., 1980). High

☆ *Grant support*: Ministry of Education, Youth and Sports of Czech Republic ME-10045, Ministry of Health of Czech Republic IGA 9976-3.
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doi:10.1016/j.ejps.2011.02.004

Table 1
The evidence of antitumor activity of cimetidine.

Cancer cells proliferation
Activation of macrophages
Up-regulation of tumor suppressive cytokines
Apoptosis induction
Inhibition of tumor cell adhesion
Inhibition of E-selection expression
Inhibition of N-CAM expression via NFκB block
Angiogenesis
Inhibition of VEGF mRNA induction mediated by H_2receptor
Activation of immune system
Increasing the levels of LT-β, TNF-α, IFN-γ
Increasing the intereleukin levels (IL-2, IL-10, IL-12, IL-15)
Increasing the number and activity of NK cells
Increasing of tumor infiltration by lymphocytes (TIL)
Enhancing the antigen presenting capacity of dendritic cells
Inhibition of postoperative immunosuppression
Inhibition of postoperative alteration in lymphocyte subpopulation (T cells, T helper cells and NK cells)
Reduction of postoperative production of neutrophil elastase and IL-8

histidine decarboxylase activity (Bartholeyns and Bouclier, 1984) and rapid histamine synthesis (Grahn and Rosengren, 1970) have been demonstrated in some types of tumors. There is a reduced diamine oxydase activity in experimental and animal tumor models (Kusche et al., 1986). In humans, the blood histamine concentration is 2–3 times higher than in patients with newly diagnosed solid malignant tumors when compared to healthy volunteers (Moriarty et al., 1988). Histamine is also known to be a modulator of malignant tumor growth and has shown to be a potential growth factor for breast cancer, melanoma cells and colon cancer cell lines (Adams et al., 1994a). In the same cancers, the histamine concentrations are high, and this may be of clinical significance (Adams et al., 1994b).

The presence of large numbers of endocrine cells, such as histamine-producing mast cells within colorectal cancer tissue adversely affects the prognosis, and cancer cells that are in close proximity to mast cells are highly proliferative (Lawson et al., 1996). By similar mechanisms histamine may affect cancer cells proliferation is via H_1or H_2 receptor activation.

In a subcutaneous model of histidine-decarboxylase knockout mice, that is, mice with undetectable levels of endogenous histamine, cimetidine failed to suppress growth of the CT-26 cell line, a mouse colon adenocarcinoma (Takahashi et al., 2002). Conversely, an identical dose of cimetidine suppressed tumor growth in wild-type mice (Takahashi et al., 2001). Based upon these results, investigators reason that cimetidine acts as a histamine antagonist at the H_2 receptors through the action of histidine-decarboxylase, ultimately suppressing tumor growth.

Cimetidine significantly induces apoptosis in human colorectal cancer cells (Adams et al., 1994b), human salivary gland tumor cells in vitro (Fukuda et al., 2008), and gastric cancer both in vitro and in vivo (Jiang et al., 2010). The results of in vivo experimental studies have shown that daily administration of cimetidine in a mouse model significantly inhibit colon cancer growth by up-regulating the expression of tumor suppressive cytokines (Takahashi et al., 2001). Additionally, cimetidine has been shown to retard the growth of human melanoma in a nude mouse model and to prolong survival in tumor bearing SCID mice by directly inhibiting the proliferation of tumor cells and indirectly promoting migration of activated macrophages to tumor site (Szincsak et al., 2002a,b). The mechanisms responsible for the antiproliferative effects of H_2 receptor antagonists are likely multifactorial, and some of them may occur independently of H_2 receptor.

2.2. Cell adhesion

In our laboratory, in vitro experiments demonstrated that cimetidine can inhibit the adhesion of breast cancer cells (Bobek et al., 2003). Takahashi et al. have also demonstrated inhibition of the adhesion of human colon cancer cells to human umbilical cord cells by cimetidine (Kobayashi et al., 2000). Cimetidine treatment was particularly effective in colorectal cancer patients with tumors expressing higher levels of sialyl Lewis^X and sialyl Lewis^A antigens (Matsumoto et al., 2002). The serum levels of these ligands correlate with the metastatic potential of cancer cells and correspond with both survival time and number of metastases of patients with lung; breast and colon cancers (Satoh et al., 1997; Grabowski et al., 2000; Yamaguchi et al., 1998; Nakagawa et al., 2009). Sialyl Lewis^X and sialyl Lewis^A are sialylated fucosylated tumor-associated antigens. There is a general association between the expression of these antigens on tumor cells and poor prognosis due to tumor progression and metastasis (Dennis and Laferte, 1987; Hakomori, 1996; Kim and Varki, 1997; Takada et al., 1993).

E-, P- and L-selectins are well-known vascular receptors for certain sialyl Lewis$^{X/A}$ antigens containing mucin-type glycoproteins found on leukocytes and endothelium (Varki et al., 1994; Kansas, 1996). Earlier studies hypothesized a simple model whereby malignant cells would be recognized by E- or P-selectin on endothelial cells, thus permitting extravasation from the bloodstream into metastatic sites. Carcinoma cells expressing these sialylated mucins can interact with platelets, leucocytes and endothelium via the selectins (Fig. 1).

Cimetidine is also an inhibitor of E-selectin (Kobayashi et al., 2000). Several anticancer drugs including 5-fluorouracil, doxorubicin, and cisplatin, increased E-selectin expression. Cimetidine has been shown to inhibit the increase in E-selectin expression by anticancer drugs at the protein level, without affecting its expression at the mRNA level (Kawase et al., 2009). Thus, a major mechanism of cimetidine action in cancer may be due to inhibition of E-selectin-mediated platelet coating of tumor cells during the initial phase of the metastatic process. E-selectin-dependent interactions represent a critical step in cell extravasation from the circulation. Cimetidine may prolong the circulation period of cancer cells in bloodstream by aggravation of cancer cell adhesion to endothelium and platelets. As a result of this, cimetidine may make the tumor more vulnerable to the cytotoxic action of NK cells (Zhang et al., 2010).

2.3. Angiogenesis

Histamine plays an important role in the regulation of angiogenesis associated with promotion of tumor progression (Norrby, 2002; Falus and Meretey, 1992). Vascular endothelial growth factor (VEGF) has been recognized as the most important growth factor involved in angiogenesis induced by numerous cytokines, as well as angiogenesis induced by hypoxic and ischemic stress (Shibuya, 1995). VEGF has been found to increase in vivo angiogenesis and vascular permeability, in vitro proliferation and migration of endothelial cells, protease production in endothelial cells, and expression of intercellular adhesion molecules on endothelial cells. In addition, VEGF overexpression has been detected in many human solid tumors (Ferrara and Davis-Smyth, 1997) and inhibition of the VEGF signal pathway was observed to prevent tumor angiogenesis, suppressing tumor growth (Millauer et al., 1996; Niethammer et al., 2002).

Recent studies have also revealed that histamine directly induces VEGF mRNA expression in granulation tissue by binding

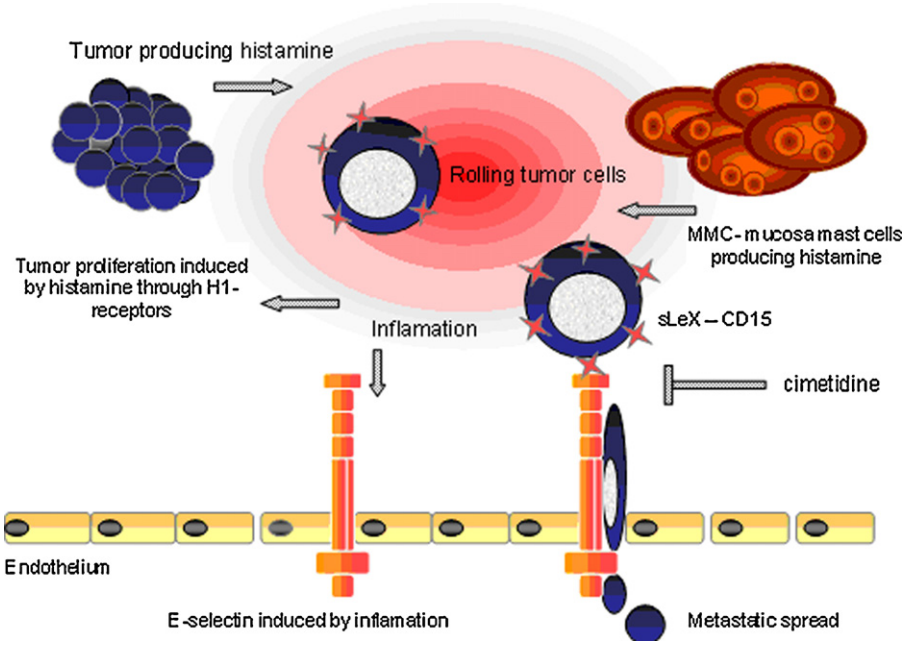

Fig. 1. Cimetidine impact on tumor cell rolling.

to H_2 receptors (Ghosh et al., 2001). In vivo angiogenesis modelling demonstrated that the adenylate cyclase/protein kinase A signaling pathway, which is involved in H_2 receptors signaling, enhanced angiogenesis via VEGF induction (Amano et al., 2001). Kobayashi et al. reported that cimetidine blocked endothelial cell E-selectin expression, a compound that plays an important role in VEGF-induced angiogenesis (Tomita et al., 2003). Tomita and colleagues demonstrated that treatment with H_2-receptor antagonists, cimetidine and roxatidine, suppressed VEGF protein expression in implanted tumor tissue, including suppressing angiogenesis in the tumor tissue. (Tomita et al., 2003) Few microvessels and many necrotic areas were observed in tumor tissue specimens obtained from mice treated with H_2-receptor antagonists. Both H_2-receptor antagonists markedly suppressed tumor angiogenesis. The anti-angiogenesis effect of cimetidine is additionally mediated by suppression of platelet derived endothelial growth factor (Chihara et al., 2009).

3. Immunity

There is increasing evidence that histamine plays a modulatory role in the regulation of tumor immunity. Increased amount of histamine may have some effects on the local cytokine expression in a variety of immune cells infiltrating the tumor tissues. Cancer patients show higher levels of suppressor lymphocyte activity than normal controls, which can be restored to baseline with cimetidine treatment (Morris and Adams, 1995).

Histamine has inhibitory effect on immune response (Beer and Rocklin, 1984; Lima and Rocklin, 1981; Rocklin et al., 1983; Uotila, 1993) via H_2 receptors (Black et al., 1972). T suppressor cells, part of the regulatory arm of the immune system, can express histamine receptors on their surface (Melmon et al., 1972; Osband and McCaffrey, 1979; Burtin et al., 1982). Histamine is capable of suppressing the immune response by activating these T suppressor cells (Rocklin et al., 1979) as well as suppressing the generation of cytotoxic T lymphocytes (Khan et al., 1989). Through this process,

Table 2
Clinical studies with anticancer effect of cimetidine in patients with cancer.

Study by	Tumor, number of patients	Cimetidine treatment	Results	Reference
Burtin et al.	Gastric cancer	Cimetidine, 800 mg/day	Prolonged survival in group treated by H_2 receptor antagonists (173 vs. 26 days)	Burtin et al. (1988)
Tonnensen et al.	Gastric cancer (n = 181)	Cimetidine, 800 mg/day	Prolonged survival particularly in advanced stadium	Tonnesen et al. (1989)
Adams and Morris et al.	Colorectal carcinoma	Pre- and postoperative treatment by cimetidine, 800 mg/day	Prolonged survival in cimetidine group (7 vs. 41%)	Adams and Morris (1994)
Matsumoto et al.	Colorectal cancer	Cimetidine, 800 mg/day for 1 year	Prolonged survival in cimetidine group (in colon cancer 3.7 vs. 32% and in rectal cancer 0 vs. 46.7%)	Matsumoto (1995)
Svensen et al.	Colorectal cancer, Dukes C stage (n = 192)	Cimetidine, 800 mg/day for 2 years	Prolonged survival in subgroup of curatively operated patients with cimetidine	Svendsen et al. (1995)
Kelly et al.	Colorectal carcinoma (n = 125)	Preoperatively treatment by cimetidine, 800 mg/day and 400 mg/day	Short course of preoperative treatment with cimetidine does appear to have an effect on patient survival.	Kelly et al. (1999)

the production of interleukin-2 (IL-2) and interferon-γ (IFN-γ) is inhibited in cultured human T lymphocytes, all of which can be reversed by H_2 receptors antagonists. One function of IL-2 is to increase the number and activity of NK cells. (Furuta et al., 2008; Nielsen et al., 1991) The successful improvement in NK cell activity after in vitro incubation with IFN-α and IL-2 led to clinical studies wherein NK cells of patients with advanced cancer were activated by human recombinant IL-2 (rIL-2) (Djeu et al., 1982; Faist et al., 1988).

Cimetidine treatment further significantly increased the levels of lymphotoxin-β (LT-β), tumor necrosis factor-α, (TNF-α), IFN-γ, interleukin 10 (IL-10), interleukin-12 (IL-12) and interleukin-15 (IL-15) (Takahashi et al., 2001) in the tumors. Each of these cytokines are known to suppress tumor cell proliferation in vivo and in vitro (Morris and Adams, 1995; Browning et al., 1996; Hazama et al., 1999; Hock et al., 1993; Faist et al., 1988).

Cimetidine treatment enhances tumor infiltrating lymphocytes (TILs) response at the tumor site. TILs have been found to be the highly effective tumoricidal T-lymphocytes (Rosenberg et al., 1986; Rosenberg, 2001), and TIL-treatment may decrease the relapse rate and prolong the survival of a subpopulation of stage III melanoma patients with one positive lymph node (Moertel et al., 1990; Monson et al., 1986), and the overall survival of stage IV gastric and colorectal cancers (Kono et al., 2002), Regression of metastatic tumors in the lung, liver and lymph nodes in patients with advanced melanoma after lymphodepletion has been induced by cimetidine (Dudley et al., 2002). Cimetidine additionally enhances the antigen presenting capacity of dendritic cells (Kubota et al., 2002).

Cimetidine has the most potent antioxidative activity of well-known hyodroxyl (–OH) scavengers including mannitol and dimethyl sulfoxide (Uchida and Kawakishi, 1990; Tamion et al., 2000). This antioxidative activity reduces proinflammatory cytokines production.

4. Postoperative immunosuppression

A successful operation can remove tumor that is inherently immunosuppressive. Evidence suggest that surgical patients undergo a period of immunosuppression immediately after surgery, the length of which depends on many factors including the general status of the patients, extent of the operation itself, and preoperative treatment. Previous studies demonstrated that T helper cells decreased and T suppressor cells increased significantly as early as 1 day after surgery (Hansbrough et al., 1984; Nichols et al., 1992; Espi et al., 1996). Many studies also confirm that surgery for patients with lung cancer (Leaver et al., 2000), gastric cancer (Sato et al., 2002; Yao et al., 2002), esophageal cancer (van Sandick et al., 2003), and colorectal cancer (Braga et al., 2002; Wang et al., 1999) induce immediate severe immunosuppresion. This immunosuppression may increase the chance of accelerated growth of residual tumors, micro-metastases and circulation cancer cells already present at the time of surgical resection (Yamashita et al., 2002). Patients with advanced TNM stage tumors have more profoundly decreased immune cells activity than patients in early stage of tumor. The activity of T cells, T helper cells and NK cells did not return to baseline level 10 days after curative resection (Lin et al., 2004). Therefore, postoperative immunosuppression may be one major contributing factor of post operative recurrence and metastasis. By contrast, patients treated by cimetidine for 1 week showed a slow but steady increase in total T cells, T helper cells and NK cells. Absolute numbers remained lower than those found in normal controls, though such reduction was a positive balance was reached after 10 days with cimetidine treatment.

Hansbrough et al. (Hansbrough et al., 1985) showed that cimetidine can prevent postoperative alterations in the lymphocyte subpopulation. Many studies have indicated that this effect is mediated by activation of a subgroup of T-suppressor-cytotoxic cells (CD8) bearing H_2 receptors. Beer and Rocklin showed that activated CD8 cells produce a soluble cytokine named histamine-induced suppressor factor (HSF) which has been implicated in inhibiting the T-helper-inducers cells (CD4) from producing IL-2, either directly or through PGE_2 and thromboxane 2 released by activated monocytes (Rocklin et al., 1983). They documented IL-2 reduction after surgery (Akiyoshi et al., 1985) injury (Mannick, 1987), or burns (Wood et al., 1984) which may be a crucial step towards postoperative impairment of the immune system. Tayama and colleagues demonstrated that perioperative high doses of cimetidine reduce postoperative production of neutrophil elastase and intereleukin-8 (IL-8) (Tayama et al., 2001). IL-8 can activate neutrophils and increase endothelial cell permeability associated with CPB (Kalfin et al., 1993) and can also stimulate unwanted histamine release (Wan and Yim, 1999; Wan et al., 1997).

5. Clinical studies (Table 2)

Cimetidine has been in use to treat gastric disorders since 1970s. Prior to the advent of stronger anti-emetics, this drug was also prescribed to treat the nausea associated with chemotherapy. The first studies suggesting that cimetidine might be effective against cancer were published in the late 1980s.()

In 1988 it was observed that cancer patients who had been treated with cimetidine had a significantly better response compared with those who had not. Burtin et al. found that a course of cimetidine or ranitidine combined with subcutaneous histamine improved survival of gastric cancer patients. They survived six times longer (173 ± 113 days) than patients receiving palliative treatment with barbiturates or analgesics (26 ± 16 days). This result has led investigators to study the effects of cimetidine in treatment of various neoplasms.

Another multicentric, randomized, double-blind, placebo controlled study by Tonnesen et al. included 181 patients and showed that cimetidine at normal therapeutic dosage (800 mg/day) also significantly prolonged the survival of gastric cancer patients, particularly in patients with stage III or IV of the disease (Tonnesen et al., 1989).

Adams and Morris found that the immunosuppressive effect of surgery for colorectal carcinoma was reduced by preoperative and short postoperative (2 days) treatment with cimetidine (800 mg/day). They reported a survival advantage for patients with Dukes A, B and C tumors. At a median 30-months follow up period, the 3-year mortality in the 7-day cimetidine treated patients was only 7% as compared with 41% for the non treated patients (Adams and Morris, 1994).

Matsumoto performed a randomized, controlled study involving patients with colorectal cancer. One group of patients received cimetidine (800 mg/day) and 5-fluororuracil (150 mg/day) for approximately 1 year beginning 2 weeks post operatively, while the patients in the control group received only 5-fluorouracil. At a mean 31-months follow-up period, the 4-year survival was significantly higher in the cimetidine treated group than in the untreated group. For patients with colon cancer mortality was 7% in the treated group, compared with 32% in the untreated group. For patients with rectal cancer, there was no mortality in the treated group compared with 46,7% in the untreated group (Svendsen et al., 1995).

A study performed by Svendsen et al. involved 192 patients who underwent surgery for Dukes C colorectal carcinoma. Randomized administration of cimetidine was started within 3 weeks after surgery at a twice-daily dose (total dose 800 mg/day), for a period of 2 years. No survival advantage was observed among

patients classified under non-curative resection ($n = 41$). Among the patients classified under curative resection ($n = 148$) survival was prolonged by cimetidine only in patients with Dukes C carcinoma, but not for the group as a whole (Matsumoto, 1995).

Kelly et al. performed a randomized study involving 125 patients with colorectal carcinoma undergoing elective colon or rectal excision and receiving either placebo or cimetidine (800 or 400 mg/day) preoperatively for 5 days. There was a significant difference between the 800 mg group and placebo group, with the effect of cimetidine most obvious in patients whose tumor had inconspicuous lympholytic infiltrate (Kelly et al., 1999).

Therapy with cimetidine for advanced renal cell carcinoma (RCC) was performed in studies in combination with Coumarin, or interferon-α. Majority of these studies demonstrated a significant benefit from administration of cimetidine. High-dose cimetidine (2400 mg/day) was administered to 38 patients with metastatic RCC; 2 demonstrated a complete response (Inhorn et al., 1992). Marshall et al. reported 3 complete and 11 partial responses in 42 eligible patients with metastatic RCC given cimetidine plus coumarin (response rate 33%) (Marshall et al., 1987). Dexeus et al. (1990), however, noted a response rate of only in 50 patients. Using the same agents and schedule combined therapy of interferon-α and cimetidine in 37 patients, there was a complete response in 7, a partial response in 8, and stable disease in 12, and progression in 10. The objective response rate was 41%. Lung metastasis showed the best response to combined therapy. The 5-year survival rates for patients with and without response, and overall were 74, 20 and 41%, respectively. Tatokoro et al. reported case studies of metastatic RCC in which combination treatment of cimetidine, cyclooxygenase-2 inhibitor (meloxicam), and a renin–angiotensin system inhibitor (ciletexil) showed partial remissions (Kinouchi et al., 1997). Histopathologically, high grade tumors had a better response to combined therapy than did low grade tumors (Tatokoro et al., 2008).

6. Conclusion

Local production of histamine may form an abnormal expression pattern of cytokines via H_2 receptors, which may result in the suppression of tumor immunity. Clinical and preclinical studies have shown antitumor and anticancer properties of cimetidine. These attributes are mediated by inhibition of tumor cell adhesion, antiangiogenesis and activation of immune system. Surgery itself reduced cellular immunity, but can be diminished as a result of cimetidine treatment. Summarizing these results, there is reason to suspect that cimetidine may provide a moderate survival benefit to patients with cancer.

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