Does Cimetidine Improve Prospects for Cancer Patients?

A Reappraisal of the Evidence to Date

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Key Words

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Abstract

Background: Evidence first appeared in 1988 that cimetidine as an adjuvant may improve the survival of severely ill gastro-intestinal cancer patients when given peri- or postoperatively. Since then, several studies have appeared which suggest an anticancer activity for cimetidine, although few attempts have been made to corroborate their findings in large, placebo-controlled, double-blind studies. **Method:** We reviewed the literature concerning cimetidine's potential anticancer activity, particularly with regard to gastro-intestinal cancers. **Results:** Most studies suggest that cimetidine may improve the outcome in cancer patients by a three-pronged mechanism involving (1) inhibition of cancer cell proliferation; (2) stimulation of the lymphocyte activity by inhibition of T cell suppressor function, and (3) inhibition of histamine's activity as a growth factor in tumours. **Conclusion:** Bearing in mind the experimental evidence, as well as the potential and excellent safety profile of cimetidine, more studies are required and justified to clarify cimetidine's protherapeutic activity.

Introduction

At the time of its introduction in the late 70s for the treatment of upper gastro-intestinal (GI) tract ulcer disease, cimetidine, the first registered H₂ receptor antagonist, was rarely considered as an agent which could be applied in spheres other than its main intended area of use. Indeed, a primary concern during the early days was whether H₂ receptor antagonists, by virtue of their acid-inhibitory activity, increased the risks of developing GI oncological disorders [1]. The risk for gastric cancer is higher amongst patients with conditions which bring about gastric hypo-acidity, and hypo-acidity favours the bacterially mediated formation of carcinogenic N-nitroso compounds [2].

Indeed, one of the first developed H₂ receptor antagonists, tiotidine, had to be abandoned when preclinical toxicity tests revealed that this agent increased the incidence of gastric tumours in rats [3]. Over the years, however, cimetidine has proven itself as an extremely safe medication with a highly specific mode of action. Regarding any potential carcinogenic activity, there is no substantial evidence to show that long-term use of cimetidine (>10 years) is associated with any dangers in this respect [4]. Although cimetidine remains one of the most commonly prescribed medications in the world today, the question

of its potential anti-oncological activity has only rarely been delved into. Many perhaps feel that any such activity would have revealed itself long before now, but there is reason to suspect that this should not be the case, especially since this activity appears to be expressed preferentially by cimetidine, and not other H₂ receptor antagonists. Furthermore, it also appears that for optimal activity it may require an adjuvant, the benefits of which would not have been revealed during the course of the extensive 'phase IV' experience acquired to date.

The first reports on the anticancer activity of cimetidine appeared at the end of the 1980s; since then it has been suggested to be effective against a number of tumours including renal carcinomas, melanomas, gastric carcinomas, and colorectal carcinomas.

This review shall provide a presentation of the currently available clinical evidence that suggests cimetidine's anticancer properties particularly in the GI tract; it shall also discuss its proposed mechanisms of action. The data available are not sufficient to perform a meta-analysis, since the individual study designs are too heterogeneous, in order to make meaningful comparisons. It will become clear, however, that cimetidine is a worthy candidate for further investigation, especially considering its high biocompatibility which allows it to be administered without fear of any serious side effects amongst most individuals.

Clinical Evidence for Effectiveness

The first reports suggesting a beneficial effect of cimetidine in GI cancer appeared in 1988, when Burtin et al. [5] found that an ad mortem course of cimetidine (1–1.2 g/day) or ranitidine (450–900 mg/day) combined with subcutaneous histamine (up to 4 mg/day) improved survival of gastric cancer patients to the extent that they survived six times longer (172 ± 113 days) than patients receiving palliative treatment with barbiturates or analgesics (26 ± 16 days, $p < 0.00001$ by *t* test). In all, 65 patients were involved in this randomized study, selected because their condition contra-indicated all other forms of therapy (surgery impossible, ineffective radio- or chemotherapy). The morbidity was found to be dependent upon whether patients were taking their therapeutic regimen, since the conditions of 4 patients deteriorated when they spontaneously discontinued and improved again upon recontinuation. Laboratory findings also improved, albeit non-uniformly, and there was an apparent stabilization of tumour size in most cases. Although that experimental

design did not allow an identification of the substance (or substances) responsible for the effect, another multicentre, randomized, double-blind, placebo-controlled study by Tonnesen et al. [6] involving 181 patients showed that cimetidine on its own at a normal therapeutic dosage (800 mg/day) also prolonged the survival of gastric cancer patients significantly, particularly in patients with stage II or IV of the disease. This study included both non-operated patients (i.e., non-resectable tumours) and palliative or radically resected patients. In a case study by Taylor et al. [7], even a complete healing was found after 3 weeks of treatment with cimetidine. This study could not of course ascertain whether this rapid healing was due to the cimetidine, but it did represent a remarkable improvement which otherwise could only be explained by spontaneous remission.

While an effect upon gastric disease (including cancer) might be expected for any agent, the primary site of action of which is the stomach, there have now been three studies which have reported a beneficial effect of cimetidine on colorectal cancer, the first significantly by Adams and Morris [8] who have been the greatest proponents of cimetidine's use in this therapeutic area. Initially, they found that the immunosuppressive effect of surgery for colorectal carcinomas was reduced by a 5-day pre- and 2-day postoperative treatment with cimetidine (800 mg/day). Somewhat surprisingly, however, they also reported a survival advantage for patients with Dukes A, B and C tumours. At a median 30-month 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. The study was prospective, randomized, and placebo-controlled, involving 34 patients, and the most significant laboratory finding was that the patients treated with cimetidine had a higher rate of lymphocyte infiltration into the tumours (67% in treated patients, 24% in controls). This was important because lymphocyte infiltration in all the patients in the study correlated with survival (56% lymphocyte response in survivors, 19% in non-survivors). All in all, this study showed a remarkable effect from a surprisingly short course of cimetidine treatment.

In the following year, Matsumoto [9] also performed a randomized, controlled study involving 64 patients, whereby one group of colorectal cancer patients received cimetidine (800 mg/day) and 5-fluorouracil (150 mg/day) for about 1 year starting 2 weeks after the operation, while the patients in the control group received only fluorouracil. At a mean 31-month follow-up, period, the 3.9-year survival was significantly higher in the cimetidine-treated

group than it was in the untreated group (colon cancer: mortality in the treated group 3.7%, in the untreated group 32%; rectal cancer: mortality in the treated group 0%, in the untreated group 46.7%).

In the same year, somewhat disappointing results were obtained by the group of Morris and Adams [10] when they, in a manner similar to that of Matsumoto [9], investigated the effects of continuous cimetidine and fluorouracil plus folinic acid versus chemotherapy alone on metastatic colorectal cancer. They observed no significant difference in survival between the groups (total study size 35 patients). The authors attributed their lack of success in demonstrating an effect to the small size of the study which did not have the power to show even a moderate increase in survival. A larger study performed by Svedsen et al. [11], however, revealed a tendency towards a reduced mortality in patients who had undergone surgery for Dukes stage C carcinoma. This study involved 192 patients from three centres who were classified as having been either curatively or non-curatively operated for adenocarcinoma of colon or rectum. Randomized administration of cimetidine was started within 3 weeks after the cancer operation, at a twice-daily dose (400 mg each) and for a period of 2 years. No survival advantage was observed amongst patients classified as 'non-curatively operated' when they had taken the cimetidine ($n = 41$). Amongst the patients classified as 'curatively operated' ($n = 148$), however, there was a survival conferred by cimetidine to patients who had been operated on for Dukes stage C carcinoma, but not to the group as a whole.

Summarizing these results, there is reason to suspect that cimetidine, given either perioperatively for a short period or postoperatively over a longer period, may provide a moderate survival benefit to patients who have been operated on for colorectal carcinomas. The optimum conditions for bringing about such an effect, however, remain to be established and might presumably be assisted by gaining a more detailed understanding of how this substance functions.

One recently performed study found that treatment with ranitidine alone could not confer a statistically significant survival advantage in operated, seriously ill gastric cancer patients ($n = 222$) [12]. However, the dose of ranitidine used was lower than that used in other studies [5], and the agent was only given postoperatively and by orally [12]. Furthermore, patients were also included in the analysis for whom a decision was made not to operate, presumably because their survival chances were considered very poor. Moreover, the authors did not rule out

that a larger study might reveal a significant survival benefit. More importantly, as the rest of this review shall bear out, there is some evidence that cimetidine may be more effective in bringing about antitumour activity than other H_2 receptor antagonists.

Experimental Studies on Cimetidine in Colorectal Cancer

Direct experimental studies investigating the effects of H_2 receptor antagonists on cancer growths in laboratory animals are relatively rare in the literature, and most of these have been performed by the groups of Adams and Morris following their initial clinical findings mentioned above. In their first study [13], cimetidine inhibited colon cancer proliferation and retarded early tumour invasion in rats in which colon cancer had been induced by a 10-week course of dimethylhydrazine. In a culture study on four different colorectal tumour cell lines, histamine was found to stimulate [3H]thymidine uptake in two cell lines [14]. This effect was reversed by cimetidine, but not diphenhydramine. The cyclic-adenosine monophosphate production, a marker of activation of H_2 -receptor-dependent adenylate cyclase, was also stimulated by histamine in a manner which was inhibited by cimetidine. When these cell lines were grown in nude mice as subcutaneous xenografts, cimetidine had a significant dose-dependent growth-inhibitory effect. The histamine-stimulated tumour growth in vivo was also inhibited by cimetidine. These results as a whole would seem to suggest that the two colorectal carcinoma cell lines possess H_2 receptors and that histamine is a growth factor acting via the H_2 receptors. This property was not uniform amongst all the colorectal carcinoma cell lines tested, and this suggests some heterogeneity in the genetic makeup of a specific human cancer condition. In another study [15], the authors compared the effects of ranitidine and cimetidine on the growth of the two responsive cell lines both in vivo and in vitro. Curiously, ranitidine did not seem to exert most of the effects mentioned above brought about by cimetidine, an observation which would argue against H_2 receptors playing a role in the effects of cimetidine, since ranitidine is marginally more potent as an H_2 receptor antagonist.

In a study by another group [16], histamine stimulated the growth of tumour cells implanted into nude mice, a process which was reversed by application of cimetidine. This effect, however, was only seen with the gastric and not with the colorectal cancer cell lines tested. Curiously,

Table 1. Inhibition of cell proliferation by the H₂ antagonists cimetidine, ranitidine and famotidine

Cell line	Cimetidine µg/ml	Ranitidine µg/ml	Famotidine µg/ml
Gastric carcinoma 23132/87	49.6 (38.2–61.2)	>1,000	1,522 (1,491–1,553)
Gastric carcinoma 3051/90	73.9 (53.6–94.2)	>1,000	3,400
Hepatoma HepG2	102 (97.5–106)	>1,000	665 (636–594)
Colorectal carcinoma Caco-2	228 (181 – 276)	>1,000	>1,000

Cell proliferation was measured by neutral red uptake. Provided are the IC₅₀ values with the 95 % confidence limits (in parentheses).

one of the colorectal cell lines tested, C170, was the same cell line investigated by Adams et al. [14] which was found by them to be responsive to cimetidine. The authors suggested that in gastric tumours, histamine acts as a growth factor, the effects of which could be reversed by cimetidine, presumably by an H₂-receptor-mediated mechanism.

In reviewing these results, it seems possible that cancer cells expressing H₂ receptors may be subject to growth stimulation by histamine and that cimetidine may reverse this effect. This phenomenon does not seem to be universal amongst all types of colorectal cancer and may represent an unnatural expression of receptors which may also come into effect in other types of cancer. Many questions and anomalies concerning the in vivo and in vitro effects of cimetidine and other H₂ receptor antagonists, however, remain to be answered and addressed.

Possible Mechanisms of Action

Inhibition of Histamine Effects

The ability of cimetidine to block histamine’s actions has been proposed as one mechanism of action for the H₂ antagonist. Histamine is a growth factor not only for some GI cell lines, but also for breast cancer and some melanoma cell lines [17]. In some cancers, the histamine concentrations are high, and this may be of clinical significance [18]. The presence of large numbers of endocrine cells within colorectal cancer tissue (particularly histamine-producing mast cells) adversely affects the prognosis, and cancer cells which are close to mast cells are highly proliferative [19].

A likely mechanism through which histamine may affect cancer proliferation is via H₁ or H₂ receptor activation. While some reports have shown that a number of non-gastric parietal cell types possess H₂ receptors (by competitive radioligand binding assay – brain cells [20] and immune cells [21] –, there have not been any reliable reports confirming their presence in colorectal or colorectal carcinoma cells. Moreover, as the information presented in the previous section showed, studies with colorectal carcinoma cells [15] indicated that ranitidine and cimetidine differed in their effects upon colonic cancer growth, both in vivo and in vitro.

Experiments by our group on human tumour cells in culture have shown that cimetidine inhibits the proliferation of a colorectal (Caco-2) and two gastric carcinoma derived cell lines in a dose-dependent manner [22] (table 1). The dose range over which it was half-maximally effective was between 50 and 228 µg/ml, corresponding to a local concentration of between 10⁻⁴ and 10⁻³ M, substantially higher than the known affinity which cimetidine shows for its receptor. Famotidine and ranitidine were only effective at much higher concentrations (IC₅₀ >1,000 µg/ml; table 1). All these observations would seem to contradict a role for H₂ receptors in bringing about direct inhibitory effects on the cancer cells. Another study using gastric cells showed that cimetidine dose dependently inhibited the histamine-stimulated proliferation of these cells, while famotidine and ranitidine exerted no significant effects over the same concentration range (up to 10⁻⁶ M) [23].

Taken as a whole, these observations would suggest that cimetidine’s effects are relatively specific to it and may for the most part be unrelated to its capacity as an H₂ receptor antagonist, at least with regard to direct effects on cancer cells. It is conceivable indeed that cimetidine might reverse the effects of histamine not by antagonizing it, but by bringing other effects into action which may work against the histamine-stimulated proliferation.

Immunological Interactions

Over the years, it has become increasingly clear that cimetidine exerts immunological effects. Histamine causes proliferation and activation of T lymphocyte suppressor cells and in this manner acts to inhibit lymphocyte function [24]. These effects are mediated by high-affinity H₂ receptors (confirmed by receptor-ligand-binding studies) and are blocked both in vitro and in vivo by H₂ antagonists [21]. H₂ antagonists also stimulate interleukin 2 production and enhance natural killer cell activity, both of which are associated with an increase in immunological

activity [24, 25]. The levels of histamine produced by many cancers are probably sufficient to bring about a local reduced immune function, and cimetidine treatment increases the infiltration of lymphocytes into primary colorectal tumours, an effect which might be due to inhibition of histamine's actions [26]. This association is significant, because it is well known that the presence of tumour infiltration is an independent indicator for an improved prognosis. Adams and Morris [8] found that pre-operative treatment with cimetidine significantly increased the proportion of colorectal cancers that elicited a lymphocyte response and that the presence of tumour-infiltrating lymphocytes was associated with a survival advantage.

GI cancer patients also show higher levels of suppressor lymphocyte activity than normal controls, and these levels can be restored to levels found in normal controls by cimetidine treatment [24]. Statistically significant lymphoblastogenesis and cell-mediated cytotoxicity *in vitro* were only observed when peripheral blood mononuclear cells obtained from gastric cancer patients were treated with cimetidine. Curiously, such effects were not seen after addition of ranitidine or famotidine which suggested either that the effect was not mediated by the H₂ receptor, or that the H₂ receptor present on the immune cells is structurally different from that present on the gastric parietal cells.

From the clinical results obtained to date concerning the effects of cimetidine in colorectal cancer, it certainly is remarkable that long-term postoperative treatment with cimetidine does not seem to confer any special advantages over a short-term perioperative treatment. The resection of most types of cancers results in a general weakening and a suppression of immune function [14]. During operation, there is a large release of histamine which can of course lead to an accumulation of this factor in tissues, particularly cancer tissues, leading to local immunosuppression. Cimetidine can prevent immunosuppression when given perioperatively [14, 27]. The main risk of an 'anergic' state during operation is that the implantation of malignant cells to other sites may occur during this phase or that tumour cells remaining after operation will have their growth accelerated. Hence an immunosuppression during operation may have an effect on long term-survival which cimetidine may counteract.

Moreover, several studies have appeared which have also shown that immunologically based therapies for various types of cancers are improved by adjuvant cimetidine therapy [28]. Cimetidine cotherapy may indeed prove to be a valuable adjuvant for the treatment of can-

cers in general, especially those for which immunological factors are decisive in determining the prognostic outcome.

Effects of Cimetidine in Non-GI Cancers

A number of small clinical trials have investigated the effects of cimetidine alone or in combination with other agents, such as leukocyte interferon, coumarin, or bis-chloroethylnitrosourea, on malignant melanoma. This condition has an extremely poor prognosis with typically short survival times, and regression rates of 20% are considered encouraging. Although combined therapies have sometimes produced regression rates of up to 30% [29], few studies have set about determining whether high-dose cimetidine (up to 1,200 mg/day) offers any real advantages over monotherapeutic strategies, and its efficacy in this respect is debated. In a medium-sized trial involving 191 patients, the best response rates amongst a number of interferon combined therapies were achieved using interferon combined with cimetidine (23%), although this effect was not significant [30]. The rationale behind adding cimetidine is that the mechanism of action of all the other adjuvants applied is immunologically based, and cimetidine, by virtue of its ability to inhibit T suppressor cells (see above), supposedly should potentiate their actions. Cimetidine on its own offers no survival advantages.

With metastatic renal cell carcinoma, the situation is very much the same as with melanoma. Usually, immunologically based therapies have been combined with cimetidine, and the contributions of cimetidine have not been adequately controlled. The condition, again, has a poor prognosis and does not respond well to intervention. Response rates as high as 33.1% have been reported with combined coumarin and high-dose cimetidine therapy [31], although much lower rates have also been reported. A recent report revealed a response rate of 40% to combined interferon and cimetidine therapy with an overall 5-year survival of 41% [32], however, another study found that adding coumarin and cimetidine to interferon did not increase response rates or survival over interferon alone [33].

Interestingly, one study [34] reported that a small proportion of patients (5%) responded with long-term remission to a cimetidine monotherapy. A case study also reported a complete response of a lung metastasis to cimetidine monotherapy.

The problem of performing controlled studies to determine the effects of cimetidine on its own versus a combined immunotherapeutic strategy is essentially ethical. Such therapies have usually been applied as last-ditch measures for seriously ill patients. Can a physician justify omitting the use of a biologically harmless drug when there is a reasonable possibility that it might enhance the effectiveness of another therapy?

Concluding Remarks

There is growing evidence that H₂ receptor antagonists, and cimetidine in particular, are effective in improving the prognostic outcome of GI and other forms of cancer. While there is still some uncertainty as to how a direct effect on cellular proliferation may play a role in

bringing about this effect, the immunological effects of cimetidine seem to be distinct and may be the most important in conferring this survival advantage. The role of 'classical' H₂ receptors in bringing about the discussed effects is unsure, since other H₂ receptor antagonists appear to be much less effective, although they are more potent against the gastric parietal H₂ receptor. Particularly striking is the fact that a short peri-operative course of treatment is sufficient to bring about its clinical effects. More studies need to be performed to determine the optimum mode for treatment which may involve a combined short peri-operative and a long postoperative course. Since the first studies appeared concerning the clinical effects of H₂ receptor antagonists in GI cancer, there have been no extensive studies which have corroborated these findings. Bearing in mind the potential and safety profile of cimetidine, more studies are required and justified.

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