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Clinical Improvement in Advanced Cancer Disease After Treatment Combining Histamine and H2-Antihistaminics (Ranitidine or Cimetidine)

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Abstract—*In a randomized study 31 patients with advanced cancer disease in whom classical anticancer therapy had been abandoned received a daily combination of subcutaneous histamine and oral H2-antihistaminics.*

In 27 patients, treatment induced a marked clinical improvement as shown by a large rise in performance status (Karnofsky scale). Ten patients were still alive 3–14 months after initiation of treatment. Average survival in the 31 treated patients (172 ± 113 days) was significantly longer than in 34 non-treated patients with similar advanced cancer (26 ± 16 days, P< 0.00001). In six treated patients, the size of liver and lung metastases decreased. Histamine was perfectly tolerated up to 4 mg/day.

INTRODUCTION

A GREAT number of experimental results have demonstrated that mast cells and basophils as well as their products of degranulation (histamine, serotonin and peroxidases) have a protective effect against tumours [1–3]. The incidence of primary tumours [4] and grafted tumours [5] was found to be higher in genetically mast cell deficient mice (W/W^v) than in their litter mates +/+ having a normal mast cell number. Moreover in fibrosarcoma-bearing mice, decreased tumour growth and lengthened survival were obtained by daily intraperitoneal injections of histamine [6]. The beneficial, although transient, effects of histamine were potentiated by combination with H2 receptor antagonists [7]. The antitumour activity of this combined treatment was attributed to the vascular activity of histamine (H1 receptors) [8] and the immunologic effects of H2 receptor antagonists [9, 10]. Even used alone, H2 receptor antagonists have been shown to have antitumour activity, particularly in increasing survival in rodents [7, 11–13]. However, other authors did not find such activity [14, 15]. In humans, an antitumour effect of cimetidine has been described, used alone [16, 17] or in combination with coumarine [18] or with interferon [19–21]. Finally a decrease in blood histamine levels in advanced cancer patients was documented by our group [22].

These experimental and clinical results led us to undertake treatment of patients with advanced cancer by a combination of histamine and H2 receptor antagonists (cimetidine or ranitidine). Preliminary results obtained in seven patients showed a marked improvement [23]. Then nine other patients were treated without randomization. For 3 years, 65 patients have been included in a randomized study. The treatment induced a clinical and biological improvement and a lengthened survival.

MATERIALS AND METHODS

Seventy-four patients were included in this study. All of them were hospitalized in the same nursing home for advanced cancer disease. They were classified into three categories: large primary tumour without known metastases, primary tumour and systemic metastases and metastases appearing after removal of the primary tumour. The distribution of these patients and the localization of the primary tumour are shown in Tables 1–5. Classical anticancer therapy had been abandoned, i.e. surgical exeresis was anatomically impossible and previous chemotherapy or radiotherapy had been ineffective.

At admission, patients had a Karnofsky perform-

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Table 1. Untreated patients: localization of primary tumours and metastases

	Group I	Group II	Group III
Larynx	1		
Pharynx	2		1
Oesophagus	3	3	1
Stomach	2	2	
Colon		2	2
Rectum		2	2
Gall bladder	1		
Liver	1		
Pancreas	2	1	
Uterus		1	1
Breast		1	1
Prostate			1
Lymphoma	1		
Metastases	0	Liver 10 Bone 2 Peritoneum 2	Liver 6 Bone 2 Peritoneum 2 Skin 1 Lung 1

Group I. Primary tumours without known metastases: $n = 13$, 3 F, 10 M, age range 48–84 years (mean ± S.D. 61 ± 19).
Group II. Primary tumour with metastases: $n = 12$, 4 F, 8 M, age range 53–82 years (mean ± S.D. 67 ± 13).
Group III. Metastases after exeresis of the primary tumour: $n = 9$, 4 F, 5 M, age range 24–87 years (mean ± S.D. 64 ± 24).

Table 2. Treated patients: primary tumour without known metastasis

	Sex Age	Primary tumour	T	Survival (days)	Karnofsky A	Karnofsky B	ESR A	ESR B	Blood histamine A	Blood histamine B	CEA A	CEA B	Liver enzymes A	Liver enzymes B
1	M 53	Oesophagus	R	58	20	50	100	61	26	40	N			
2	M 42	Pharynx	C	72	30	50	30	20	35	40	N			
3	M 67	Pharynx	C	180	40	70	12	5	35	82	N			
4	M 49	Oesophagus	R	208	20	50	60	60	30	32	N			
5	M 91	Colon	R	234	20	70	104	61	29	90	56	60		
6	F 63	Oesophagus	R	257	20	50	140	90	22	31	N			
7	M 74	Lung	R	277	20	70	131	41	16	59	N			
8	M 60	Pancreas	R	380	30	60	60	50	46	67	N			
9	M 56	Larynx	C	232*	40	70	87	42	38	81	N			
10	M 73	Rectum	R	265*	20	60	132	125	16	45	40	8	139	83
11	M 48	Pharynx	R	358*H	30	70	87	85	52	70	N			
12	M 56	Larynx	R	443*H	30	70	58	45	79	87	N			

T: treatment; C: cimetidine; R: ranitidine.
*Still alive since x days after beginning of the treatment.
H indicates that patients went back home; A beginning of the treatment; B at the best period of improvement; ESR erythrocyte sedimentation rate; blood histamine levels: ng histamine base/ml blood; CEA N normal values < 5 ng/ml; Liver enzymes: values not shown remained unchanged whatever their levels.
●γ-GT, ○ Aph, + transaminases.

ance status scale (KPS) [24, 25] of 20 and were unable to walk, dress or wash without help. They had severe nutritional problems (loss of weight > 20% and/or prealbumin < 0.15 g/l) due to cancer itself, palliative surgery or intensive radiotherapy. Spontaneous ingesta were below 1200 cal/day. The clinical and nutritional status of 12 patients needed parenteral nutrition.

Among these 74 patients, nine were treated without randomization. Thirty-one patients admitted to the nursing home on even days of the month received our treatment while 34 patients admitted on odd days received only palliative drugs such as barbiturates and analgesics. All treated patients gave their informed consent.

In order to better assess the influence of treatment

Table 3. Treated patients: primary tumour with metastases

	Sex Age	Primary tumour	Metastasis	T	Survival (days)	Karnofsky A	Karnofsky B	ESR A	ESR B	Blood histamine A	Blood histamine B	CEA A	CEA B	Liver enzymes	
13	M 52	Pancreas	Liver	R	30 F	20	10	100	110	29	47	20	20		
14	M 69	Unknown	Liver	C	49 F	20	10	91	140	25	72	N			
15	M 68	Rectum	Liver	C	50 F	20	10	62	94	34	59	725	804		
16	F 68	Unknown	Liver	C	48	20	40	35	46	32	153	2400	6200		
17	M 80	Lung/trachea	Liver	R	57	20	50	110	97	8	38	N		742	129 ○
18	F 82	Unknown	Peritoneum	R	70	30	50	61	38	27	41	N		52	26 +
19	M 62	Colon	Peritoneum	R	76	20	60	128	48	21	53	58	790	43	18 +
20	F 76	Unknown	Peritoneum	R	85	20	40	70	50	10	19	N	N		
21	F 58	Breast	Lung	R	150	20	50	100	47	17	34	N			
22	M 69	Liver	Peritoneum	C	171	20	70	114	58	7	40	N		133	79 ●
23	F 82	Colon	Peritoneum	R	182	20	50	84	62	21	52	66	390	128	66 +
24	F 86	Ovary	Liver	R	220*H	20	50	73	59	23	63	N			
25	F 58	Bladder	Lung	R	284*H	30	70	65	49	19	49	N			

F indicates failure of treatment.
See also footnote to Table 2.

Table 4. Treated patients: metastases alone

	Sex Age	Primary tumour	Metastasis	T	Survival (days)	Karnofsky A	Karnofsky B	ESR A	ESR B	Blood histamine A	Blood histamine B	CEA A	CEA B	Liver enzymes A	Liver enzymes B
26	M 64	Oesophagus	Liver	C	22 F	20	10	47	61	28	8	21	46		
27	M 50	Oesophagus	Liver	R	250	20	50	68	59	30	32	N	N		
28	M 68	Prostate	Bone	R	90*H	30	70	25	27	15	37	N			
29	F 86	Ovary	Liver	R	120*	30	60	75	69	32	40	N			
30	F 65	Breast	Lung	C	125*	30	70	30	30	34	62	N			
31	M 88	Colon	Liver	R	301*H	30	70	92	32	67	87	90	1028	70	15+

See also footnote to Table 2.

Table 5. Treated patients: before randomization

	Sex Age	Primary tumour	Metastasis	T	Survival (days)	Karnofsky A	Karnofsky B	ESR A	ESR B	Blood histamine A	Blood histamine B	CEA A	CEA B	Liver enzymes A	Liver enzymes B
32	M 55	Pancreas	0	C	93	20	40	51	6	31	54	N		68	36 ○
33	M 81	Lymphoma	0	R	110	20	40	72	27	13	20	N			
34	M 50	Oesophagus	Liver	R	15 F	20	10	110		14	26	25			
35	F 52	Sarcoma (calf)	Liver	R	69	20	30	60	70	15	22	N			
36	M 62	Pancreas	Liver	C	152	20	50	92	78	30	62	N			
37	M 68	Lung	Bone	C	180	20	60	136	98	23	38	N	N		
38	F 61	Uterus	Liver	C-R	1090	20	70	120	85	7	10	N	N		
39	F 78	Rectum†	Lung Liver	C	116	20	40	85	50	8	127	142	160	304	198 ●
40	M 49	Rectum†	Liver	C	232	20	70	50	8	49	84	1072	90	110	57 ●

†Indicates exeresis of the primary tumour.
See also footnote to Table 2.

on clinical status and disease progression, patients were first observed during a period of at least 1 week after admission. This week of observation was excluded from the subsequent calculation of survival.

Treatment consisted of daily cimetidine (1000–1200 mg in three divided doses) or ranitidine (450–900 mg in two divided doses) for 2 days orally. On the 3rd day, subcutaneous histamine was added to ranitidine or cimetidine. Vials contained 2 mg of histamine dihydrochloride and 100 mg of glucose in 2 ml of sterile bidistilled water. This solution did not induce pain at the site of injection. The first daily dose of histamine was 0.5 mg. After verification that this dose was well tolerated, patients received 0.5–2 mg twice a day. No other treat-

ment was given, in particular H1-antihistaminics or corticosteroids.

Surveillance of the patients included daily measurements of spontaneous ingesta, weekly assessment of blood count, erythrocyte sedimentation rate, liver enzymes, blood histamine and CEA serum levels (enzyme assay, Abbott method). Liver echography and chest X-ray were performed monthly. The KPS was evaluated every week.

Statistical analysis for comparing survival of treated and untreated patients was performed with the t test. In spite of the difference in the variance σ^2, this test can be used when the number of subjects is higher than 30 in each group. We must emphasize that the use of this method decreased the difference in survival between treated and untreated patients since patients still alive must be counted as dead on 31 October 1986.

RESULTS

I. *Untreated patients* (n = 34) (*Table* 1)

The status of the untreated patients progressively declined and none showed spontaneous transient improvement, either clinically or in laboratory results. Parenteral nutrition was required for six patients and could not be interrupted. Blood histamine levels, which were always low, remained stable until death in 15 patients and decreased in 19 patients. An increase in blood histamine levels was never observed.

All the untreated patients died between 10 days to 8 weeks after the 1st week of admission. Mean survival ± S.D. was 26 ± 16 days without significant differences among the three groups.

II. *Treated randomized patients* (n = 31) (*Tables* 2–4)

Clinical data. In 27 patients, clinical improvement became evident 8–10 days after beginning treatment. KPS rose to 50 or even 70 during the best period. Patients were able to assume most of their personal care. Spontaneous ingesta increased progressively (1200 cal/day to 1800–2000 cal/day) with a concomitant weight gain (1–4 kg). In five patients parenteral nutrition could be interrupted 4–6 weeks after initiation of treatment.

In two patients with pancreatic carcinoma, pain disappeared allowing the suppression of analgesic drugs. Six patients were discharged from the nursing home. They pursued their treatment at home where they led normal lives. However, they have not resumed their occupational activities (when they had any).

Four patients spontaneously discontinued their treatment. After 15–20 days their condition worsened. Treatment was then resumed and improvement was again observed.

Laboratory data. Improvement in laboratory results was observed in some patients during the best period. Erythrocyte sedimentation rate decreased in nine patients (110 ± 15 mm to 53 ± 17 mm) and remained stable in the others. Liver enzymes (γ-GT, alkaline phosphatase and transaminases) decreased in seven patients. Prealbumin levels reached normal values in four patients and increased in 12 others. In nine patients with colorectal carcinoma, CEA levels were increased before treatment (range 20–2400 ng/ml). CEA levels remained stable in four patients and returned to normal in one patient. In four patients, treatment induced a marked increase in CEA levels (58–790, 66–390, 90–1028, 2400–6200 ng/ml) during the period of clinical improvement and stabilization of cancer. In two patients a subsequent decrease in CEA levels was observed 2 months later without return to normal values.

Initial values of blood histamine levels (expressed as ng histamine base/ml blood, mean ± S.D.) were 35 ± 15 in the group with primary tumour, 22 ± 10 in the group with primary tumour and metastases, 34 ± 12 in the group with metastases alone. These levels increased in patients during the period of clinical improvement and reached normal values (65 ± 24) in 18 patients. During the period preceding the death, blood histamine levels progressively decreased to less than 20 ng/ml.

Influence on tumour and metastases. In most cases tumour size was apparently stabilized. A decrease in tumour volume was seen in two patients with oesophageal cancer and allowed fibroscopic examination. Transient fistulization of the tumour was observed in two other patients. The size and number of metastases remained stable in most cases. However, a 30% decrease in the size of liver metastases was observed in four patients by echography and in lung metastasis for two patients by chest X-ray.

Survival. Ten patients are still alive after treatment lasting from 3 to 15 months. Despite continuation of treatment, 17 patients died after a period of clinical improvement (mean survival 162 ± 97 days, range 48–380 days). Complete therapeutic failure was observed in four patients with metastases. These patients progressively declined and died 22–49 days (mean survival 38 ± 14 days) after the beginning of the treatment. This survival was not significantly different from that observed in untreated patients.

Survival in the 31 treated patients was calculated from the 1st day of treatment until death or the end of the study (31 October 1986). The mean survival in treated patients (172 ± 113 days) was significantly longer than in 34 non-treated patients (26 ± 16 days) ($P < 0.00001$).

Tolerance. The excellent tolerance to histamine injections must be emphasized. Except in two patients with pancreatic tumour where a moderate flush was observed, injections of high amounts of histamine did not induce hypotension, flush or bronchospasm. In four patients, histamine injections were immediately followed by a slight and transient pain at the site of the primary tumour, which did not preclude successful continuation of treatment.

III. *Treated patients before randomization* (n = 9) (*Table* 5)

These patients, who were treated 3 years ago, were similar to the patients treated after randomization: sex, age, localization of the primary tumour and metastases (Table 5).

Treatment induced clinical improvement in eight patients. Survival was significantly longer ($P < 0.0001$) than in non-treated patients.

In a man with liver metastases, after resection of a rectum carcinoma, treatment induced stabilization of the size of metastases. After interruption of treatment for 2 months, the size of metastases increased with a relapse in clinical status. The reinitiation of treatment induced a restabilization.

In this group a woman with unresectable ovarian adenocarcinoma and innumerable liver metastases had a KPS which raised from 20 to 70 during treatment. The treatment was interrupted for 1 month and the KPS returned to 20. The reinitiation of treatment induced a clinical improvement (KPS 70) over 32 months. In spite of the continuation of the treatment, the clinical status declined progressively and this patient died 3 years after the beginning of the treatment.

DISCUSSION

Preliminary open trials had shown that treatment combining histamine and H2-antihistaminics induced a clinical improvement in patients with advanced cancer disease. Thus we undertook a randomized study which included 34 untreated and 31 treated patients. Our treatment induced a clinical improvement in 27 patients. Moreover, improvement in laboratory results (prealbumin, ESR, liver enzymes, CEA, blood histamine) was found in treated patients and never in non-treated patients. Another fact argues in favour of the activity of our treatment. Discontinuation of treatment in some patients induced a relapse which was reversed by a second course of treatment. Therefore, as a result of these data, all our patients are treated every day without any interruption.

The mechanisms of the beneficial effects of our treatment are not clear as yet. A direct action of histamine and H2-antihistaminics on tumour cells is questionable. Indeed, added to tumour cell cultures at concentrations varying from 10^{-12} to 10^{-3} M, neither histamine nor cimetidine and ranitidine modifies the proliferation of tumour cells [26]. Yet the *in vitro* effects on tumour cell cultures do not necessarily reflect *in vivo* effects of histamine and H2-antihistaminics on the tumours.

Two mechanisms, pharmacological and immunological, are probably involved. The stimulation of H1-histamine receptors increases vascular permeability. In fibrosarcoma-bearing mice the injection of histamine or serotonin increased the intratumoral penetration of cellular and humoural elements [8]. This treatment induced bands and foci of necrotic and haemorrhage tissue in the tumour [6, 7]. Similar mechanisms were perhaps involved in two patients whose tumour fistulized and in four patients whose CEA levels rose without any deterioration in clinical status or increase in tumour volume. It might be hypothesized that partial tumour necrosis had released intratumoural CEA into the bloodstream. The fact that histamine induced pain in four patients at the precise site of the tumour, and nowhere else, argues in favour of a local effect.

Some antitumour effects of histamine could also be due to the increase of contra-suppressor T lymphocyte activity (H1-dependent) [9]. We gave H2-antihistaminics not only to avoid gastric hypersecretion induced by histamine but also because of their antitumour effect attributed to the inhibition of T lymphocyte suppressor activity [10, 27, 28]. However, the T4/T8 ratio was normal in 19 patients before treatment and was not significantly modified by treatment (results not shown).

At present ranitidine seems as efficient as cimetidine in agreement with *in vitro* experimental data on lymphocyte response [29] and *in vivo* data on tumour growth in mice [13]. For cimetidine and ranitidine, no relationship between doses and effects could be observed.

The excellent tolerance to histamine must be emphasized. Subcutaneous injections induced neither hypotension nor flush nor bronchospasm. This decreased H1 receptor sensitivity in cancer patients was also observed for skin response to intradermal histamine. The incidence and the size of weal and flare were significantly lower in cancer patients than in non-cancer patients [30]. Experimental data support the notion that malignant tumours induce decreased sensitivity to vasoactive amines. In fibrosarcoma-bearing mice, the intensity of anaphylactic response (local or general, active or passive) was shown to be less than in normal mice [31]. The sensitivity of tumour-bearing mice to challenge with histamine and serotonin mixtures was also reduced [32]. This deficit in histamine responsiveness has been shown to favour tumour growth. It is thus possible that the injection of large

amounts of free histamine overcame this deficit in our cancer patients.

Finally, three points must be considered:

1. Treatment was applied without regard to the type of tumour and moreover in cachectic patients with advanced cancer. Future well-controlled studies should attempt to determine the indications of this treatment and its efficiency in less severely disabled patients.
2. The combination of histamine, H2-antihistaminics and chemotherapy could be interesting. Increased intratumoural penetration of antimitotic drugs could be obtained, allowing reduction of doses and side-effects while preserving their therapeutic activity.
3. Survival of tumour-bearing mice was decreased by H1-antihistaminics treatment [7]. Thus the prescription of H1-antihistaminics in cancer patients should be questioned since beneficial effects of histamine, in humans and in mice, could be attributed to the stimulation of H1 receptors.

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