DMSO

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# Oxygen-Derived Free-Radical Scavengers Prolong Survival in Gastric Cancer

**Key Words**
Oxygen
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**Abstract**

The influence of oxygen-derived free radical scavengers on survival in gastric cancer, with serosal invasion and metastases to the lymph nodes surrounding the stomach, was assessed in a prospective randomized controlled double-blind trial conducted for 5 years. To this end, allopurinol (inhibits the enzyme xanthine oxidase which is responsible for the formation of superoxide radicals and scavenges hydroxyl radicals) and dimethyl sulphoxide (DMSO; scavenges hydroxyl radicals) were used. Following potentially curative distal two-thirds partial gastrectomy, 228 patients making an uneventful recovery from surgery were randomized to the control group or to receive allopurinol (50 mg by mouth 4 times a day) or DMSO (500 mg by mouth 4 times a day). In 160 fully evaluable patients who were studied for 5 years, allopurinol and DMSO incurred a significant ($p < 0.01$) survival advantage over the whole period of study. The similarity in efficacy between allopurinol and DMSO and the fact that the only action they share is scavenging oxyradicals suggest that these radicals mediate the aggressiveness of gastric cancer by producing tissue damage, thus allowing the cancer to spread. Consequently, oxygen-derived free radicals are implicated in the mechanism of gastric cancer, and removing them provides patients with a survival advantage.

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## Introduction

The majority of gastric cancer patients have widespread disease at the time of diagnosis, consequently in a considerable proportion surgery is often palliative [1]. The overall 5-year survival of patients with gastric cancer is approximately 5% [2]. The early stages of this disease, defined as tumour limited to the mucosa and submucosa with or without lymph node metastases [3], have a 5-year survival following surgical resection of 70–90% compared with 30–40% in locally advanced stages [4–6].

After almost all non-curative gastrectomies and some curative ones, gastric cancer recurs. Over half of the patients show peritoneal dissemination followed in order of importance by distant metastases via lymphatic and/or haematogenous spread, and reappearance of the cancer at anastomotic stomata [2, 3–5]. Recently [7], it has been clearly shown that the 5-year survival rate in gastric cancer patients is inversely related to the degree of serosal invasion and that patients with this invasion at resection will develop disease recurrence. Furthermore, the presence of lymph node metastases in conjunction with serosal invasion had poor prognosis causing intraperitoneal dissemination followed by death of most of the patients within 2 years of their operation [7].

The results of adjuvant chemotherapy trials in gastric cancer are less favourable in European and Anglo-American countries than in Japan [8]. The majority of findings in Western countries leads to the conclusion that the routine application of adjuvant chemotherapy for gastric cancer cannot be recommended [8]. On the other hand, intra-operative radiotherapy has been shown to improve the survival only in patients with locally advanced gastric carcinoma [9].

Oxygen-derived free radicals are cytotoxic and play a key role in the mechanism of tissue injury [10–12]. Studies in the rat (to be published) demonstrated that these radicals are permissive for gastro-intestinal carcinogenesis. Exposure to doses of carcinogenics that are capable of producing gastro-intestinal cancer failed to exhibit any carcinogenic activity when the rat was treated with radical scavengers. Conversely, the doses of these carcinogenics which do not produce cancer under normal circumstances were allowed to do so when the overall pool of oxygen-derived free radicals was increased. It was also noted that in the rat bearing gastro-intestinal cancer scavenging oxygen-derived free radicals delays hepatic metastases and prolongs survival. These studies propose that oxyradicals are implicated in the mechanism of gastro-intestinal cancer in the rat and mediate its aggressiveness probably by producing the destruction of tissues associated with this cancer and which, in turn, allows it to spread. The present investigation was, therefore, designed to examine whether removing oxygen-derived free radicals incurs any survival advantages in patients with carcinoma of the stomach.

## Patients and Methods

*Drugs*

A 1% solution of allopurinol (Burroughs Wellcome Co., Research Triangle Park, N.C., USA) was prepared by dissolving the powder in double-distilled water containing the molar equivalent of 0.1 *M* NaOH. A 10% solution of dimethyl sulphoxide (DMSO; Sigma, St. Louis, Mo., USA) was prepared by diluting the stock solution with double-distilled water. The vehicle solution of allopurinol was given to controls. Solutions were placed in 600-ml capacity dark-coloured glass bottles of identical appearance. The patients were issued a fresh supply of solutions every 30 days and were treated with identical volumes of solution throughout the 5-year period of the study.

*Study Design*

This was a prospective randomized controlled double-blind trial conducted for 5 years on consecutive pa-

tients making an uneventful recovery from a 'potentially' curative distal two-thirds partial gastrectomy for carcinoma of the distal third of the stomach. Randomization was carried out by drawing sealed envelopes. Treatment started on the 5th postoperative day and continued to the end of the study (5 years).

*Recruitment Criteria*

Patients were considered to be suitable for the study if all the following conditions applied: (1) the carcinoma had invaded the serosa but not any contiguous structures; (2) the gastrectomy specimen showed tumour-free proximal resection lines (within 5 mm from resection lines) for at least 2 cm; (3) complete excision of all the regional lymph nodes of the stomach according to the location of cancer, i.e. lymph nodes along the greater and lesser curvatures, the supra- and subpyloric nodes, the right paracardial lymph nodes and the lymph nodes along the course of the left gastric, the common hepatic and around the coeliac arteries; (4) there were metastases to the lymph nodes surrounding the stomach but no metastases to the nodes along the main arteries including the coeliac axis; (5) the lymph node metastases were in the form of cancer cells within the lymph node system but without extension beyond the node into the perinodal fatty tissues; (6) no macroscopically evident peritoneal dissemination and no free cancer cells within the peritoneal cavity immediately after the gastrectomy (the peritoneal cavity was washed with 100 ml of physiological saline at 37 °C immediately after the gastrectomy, then 50 ml of this fluid was centrifuged, stained and examined as described in detail elsewhere [13]); (7) no evidence of hepatic or distant metastases. This means that the stage of the patients studied was $S_2$ $N_1$ $P_0$ according to the Japanese Research Society for Gastric Cancer.

Patients were not recruited into the trial if one or more of the following were present: age over 80 years; risk factors [adenomatous polyp(s) removed]; admission as an emergency failing to respond to conservative treatment or septicaemia or peritonitis on presentation; pregnancy; alcoholism; taking prohibited drugs or regularly taking any form of medication (to avoid unknown therapeutic effects and drug interactions); hypertension; diabetes; hepatic (including cirrhosis) or renal disorders; serious underlying disease – for example cardiorespiratory problems; rheumatoid arthritis or any form of collagen diseases; Zollinger-Ellison syndrome or other gastro-intestinal disorders like the irritable-bowel syndrome which would make it difficult to assess patients and the significance of their signs and symptoms; previous gastro-intestinal surgery; history of radiotherapy, chemotherapy or any malignancy; synchronous carcinomas; invasion of the abdominal wall or any adjacent organs or structures found during laparotomy; postoperative complications (cardiovascular, pulmonary – pneumonia or atelectasis –, hepatic, wound infection or dehiscence, gastro-intestinal haemorrhage, anastomotic failure, ileus, significant reflux oesophagitis or psychiatric problems); or cases with hypersensitivity to penicillin and its derivatives. Survival was measured from the time of tumour resection until death from any cause. Postoperative deaths (mortality from any cause during hospital stay irrespective of its duration) were not included in the study. Survival calculations were only carried out on patients who had died from tumour recurrence, and those dying from other causes (e.g. cerebrovascular accidents, myocardial infarction, bronchopneumonia) were excluded.

*Clinical Management*

Gastric carcinoma was diagnosed from the history, physical examination, endoscopy with biopsies and a barium meal. Other investigations were undertaken to determine the extent of the disease or to serve as a baseline for future reference, and these included: standard haematology, biochemistry measurements, urine examination, chest X-rays and liver ultrasonography. Once the diagnosis of gastric carcinoma had been made, patients were admitted to hospital and prepared for surgery: correction of any anaemia or hypoproteinaemia, and chest and lower limb's physiotherapy. At induction of anaesthesia the patients were given intravenous chemoprophylaxis, 500 mg of ampicillin and 80 mg of gentamicin, and prophylaxis against deep-vein thrombosis was by peri-operative pneumatic compression leggings. In all cases the abdomen was opened by an upper midline incision, the liver was palpated for any metastases, the various lymph node groups (surrounding the stomach, in the hepatoduodenal ligament, in the retropancreatic area, in the mesenteric root, around the left gastric, common hepatic, coeliac and middle colic arteries, and around the abdominal aorta) were carefully examined, and the peritoneum was inspected for evident dissemination. At least a 2-cm tumour-free proximal resection line was achieved, excision of all the regional lymph nodes as detailed above was carried out, gastric reconstruction was by a Roux-en-Y gastrojejunostomy, all the anastomoses were performed by double-layer continuous suturing with 2/0 polyglycolic material (Dexon), and the peritoneal cavity was examined for free cancer cells as stated above. Post-operatively patients were hydrated intravenously for at least 3 days during which period their oral intake of fluids was gradually increased. The return to solid food was not permitted before the 4th

postoperative day. The patients were supplied with special charts to mark their compliance with the therapeutic regimen and to record any adverse events.

Following discharge from hospital, the patients were reviewed every 3 months on an out-patient basis. At each visit a detailed assessment of any symptoms and possible adverse events coupled with a full physical examination, endoscopy with biopsies of any suspicious gastric mucosa, full blood counts, liver function tests and a liver ultrasound scan were performed. A chest X-ray was taken annually, unless indicated earlier.

*Ethical Considerations*

This study was approved by the Ethical Committee on Human Experimentation of the hospital, and every patient gave written informed consent.

*Study Groups*

Two hundred and twenty-eight consecutive patients with an uneventful recovery from a distal two-thirds partial gastrectomy for carcinoma of the stomach were allocated to one of three groups and treated for 5 years. In the first group patients were given the vehicle solution of allopurinol by mouth, 5 ml 4 times a day (controls). In the second group patients were given allopurinol by mouth, 5 ml (50 mg) 4 times a day. In the third group patients were similarly treated with 5 ml DMSO (500 mg) 4 times a day.

*Exclusion Criteria*

Exclusion of patients from evaluability was based on the following rules: (1) significant adverse events to the therapeutic regimen; (2) intolerance of this regimen; (3) failure to comply with the regimen; (4) concomitant treatment during the study with medicines; (5) postoperative complications or mortality occurring after randomization of the patients on the 5th postoperative day; (6) missed synchronous malignant tumours (detected up to 6 months after surgery) or occurrence of metachronous malignant tumours; (7) death from other than tumour-related causes; (8) failure to attend for or lost to follow-up. The decision to regard patients as non-evaluable for analysis was undertaken before breaking the treatment code.

*Statistical Analysis*

A sample size of 150 patients with 50 patients in each group was chosen initially. Based on a two-tailed test, such a size will detect a significant difference of 30% between active and no therapy ($p < 0.05$) with a probability of 80% for the overall sample. Because of the anticipated problems of non-evaluability of a proportion of patients inherent in a long-term study which could weaken any conclusions drawn, the aim was to enter at least 75 patients in each group.

Results are expressed as percentages or the mean ± SEM unless stated otherwise. The statistical significance ($p < 0.05$) of observed differences in percentage values was assessed using the $\chi^2$ test with Yates' correction, and the Mann-Whitney U test for non-parametric data was employed to examine whether differences in mean values were significant. Kaplan-Meier's product limit method was used to estimate the survivor functions for the three study groups. The difference between these functions was assessed using the Mantel-Cox statistics. Proportional hazard models were then used to investigate the effect of treatment on survival when account was taken of the other patient factors as covariates. Additional intention-to-treat analyses were carried out re-including the patients who were excluded from the study and using various theoretically possible outcomes to assess any influence their exclusion might have had on the conclusions of the study.

## Results

*Patient Characteristics*

Seventy-seven patients (30 women and 47 men with an age range of 41–79 years, mean 59) were randomized to the control group. Seventy-five patients (30 women and 45 men with an age range of 44–78 years, mean 58) were randomized to the allopurinol group. Seventy-six patients (27 women and 49 men with an age range of 48–80 years, mean 61) were randomized to the DMSO group. The patients excluded from evaluability are presented in table 1, and the characteristics of those remaining are shown in table 2. The three groups were well matched for age and sex, for duration of symptoms before presentation, type of presentation, weight loss and for tumour differentiation.

*General Observations*

Seventeen controls (31%), 20 patients in the allopurinol group (39%) and 16 patients in the DMSO group (30%) were smokers, and all

the men studied were social drinkers who did not indulge heavily. Ten patients in the control group (18.2%; 6 vomiting and 4 acute gastro-intestinal haemorrhage), 8 patients in the allopurinol group (16%; 3 vomiting and 5 acute gastro-intestinal haemorrhage) and 11 patients in the DMSO group (20.4%; 6 vomiting, 1 acute epigastric pain, 4 acute gastro-intestinal haemorrhage) presented as an emergency which settled with conservative treatment. The remaining cases presented with one or more of abdominal pain, dyspepsia, anorexia or signs and symptoms of iron deficiency anaemia, and the frequency of these symptoms was similar among the three groups. The mean length of symptoms for the emergency and non-emergency cases was comparable among the groups. In the non-emergency cases, iron deficiency anaemia was seen in 10 controls, in 8 members of the allopurinol group and in 11 members of the DMSO group. Of these patients, 5 controls, 4 members of the allopurinol group and 6 members of the DMSO group were given pre-operative blood transfusions, whereas the remaining patients were given oral ferrous sulphate. Consequently, the total number of patients in each group who received pre-operative blood transfusions were 9 controls (16.4%), 9 patients in the allopurinol group (17.6%) and 10 patients in the DMSO group (18.5%). During surgery, 10 patients in the control group (18.2%), 12 patients in the allopurinol group (23.5%) and 11 patients in the DMSO group (20.4%) received blood transfusions.

The overall operative mortality (death from any cause during hospital stay irrespective of its duration) was 3.1%. Of these patients 1 control died because of myocardial infarction, and 1 patient in the DMSO group died because of bronchopneumonia after randomization.

One patient in the control group (bronchopneumonia), 3 patients in the allopurinol group (1 deep-vein thrombosis and 2 wound infections) and 2 patients in the DMSO group (1 wound infection and 1 anastomotic failure) developed postoperative complications after entry into the study. One patient given DMSO and 2 patients given allopurinol were intolerant to their therapeutic regimen. Four patients given the vehicle solution of allopurinol and 5 patients in each of the remaining groups reported drug-related side-effects consisting of headache, nausea and general malaise. In addition, allopurinol treatment caused skin hypersensitivity and allergic reactions. However, these effects were severe enough to warrant cessation of treatment only in 2 controls, in 2 patients treated with allopurinol and in 1 patient treated with DMSO.

**Table 1.** Evaluability of patients

| | Control | Allo-purinol | DMSO |
|---|---|---|---|
| Total entered | 77 | 75 | 76 |
| Fully evaluable | 55 | 51 | 54 |
| Not evaluable because of | | | |
| Intolerance | 0 | 2 | 1 |
| Adverse events | 2 | 2 | 1 |
| Non-compliant | 3 | 3 | 2 |
| Prohibited drugs used | 0 | 0 | 1 |
| Failure to attend for follow-up | 5 | 4 | 5 |
| Metachronous malignancy | 0 | 1 | 0 |
| Synchronous carcinoma | 0 | 1 | 0 |
| Postoperative complications | 1 | 3 | 2 |
| Postoperative mortality | 1 | 0 | 1 |
| Died from other than cancer-related causes | 10 | 8 | 10 |
| Total not evaluable | 22 | 24 | 23 |

**Table 2.** Patient details

| | Control | Allopurinol | DMSO |
|---|---|---|---|
| n | 55 | 51 | 54 |
| Age, years | | | |
| Mean | 57 | 59 | 58 |
| Range | 42–77 | 44–77 | 48–78 |
| Women, n | 20 | 17 | 17 |
| Men, n | 35 | 34 | 37 |
| Emergency cases, n | 10 | 8 | 11 |
| Symptoms (mean), months | | | |
| Emergency cases | 1.7 | 2.1 | 1.9 |
| Non-emergency cases | 6.1 | 5.8 | 6.3 |
| Weight loss, n | | | |
| <5% | 31 | 25 | 26 |
| 5–10% | 15 | 20 | 18 |
| >10% | 9 | 6 | 10 |
| Patients given pre-operative blood transfusion, n | 9 | 9 | 10 |
| Patients given peri-operative blood transfusion, n | 10 | 12 | 11 |
| Patients given postoperativc blood transfusion, n | 3 | 3 | 2 |
| Tumour location, n | | | |
| Antrum and pylorus | 42 (76.4%) | 40 (78.4%) | 44 (81.5%) |
| Gastric stump | 13 (23.6%) | 11 (21.6%) | 10 (18.5%) |
| Tumour differentiation, n | | | |
| Good | 14 | 9 | 15 |
| Moderate | 15 | 19 | 12 |
| Poor | 6 | 7 | 10 |
| Undifferentiated | 16 | 13 | 14 |
| Signet ring cell | 2 | 1 | 0 |
| Mucinous | 2 | 2 | 3 |
| Lauren's classification, % | | | |
| Intestinal | 58 | 59 | 61 |
| Diffuse | 29 | 25 | 26 |
| Mixed | 13 | 16 | 13 |
| Lymph nodes resected per specimen (mean) | 28.2 | 32.5 | 30.7 |

*Tumour Characteristics*

Pre-operative histologic diagnosis of gastric cancer was achieved in every patient. The tumour location, its degree of differentiation, its histologic grade and the number of lymph nodes resected per specimen were comparable among the study groups. The majority of the gastric cancers studied were located in the antrum or pylorus and were differentiated adenocarcinomas (table 2).

*Recurrence*

All patients who developed a recurrence subsequently died of their disease. Over half of the patients who died in each group developed peritoneal dissemination (26 controls, 53.1%; 18 patients in the allopurinol group, 51.4%; 20 patients in the DMSO group, 55.6%), whereas distant metastases to the liver and/or lung were less common (13 controls, 26.5%; 10 patients in the allopurinol group,

28.6%; 9 patients in the DMSO group, 25%) and local recurrence at the anastomotic stoma was the least common (10 controls, 20.4%; 7 patients in the allopurinol group, 20%; 7 patients in the DMSO group, 19.4%).

*Survival*

In all the groups, most of the deaths occurred during the first 3 years following the gastrectomy (table 3). In the control group, the number of patients who were alive after 1 year (33, 60%) was significantly ($p < 0.01$) less than that at the start of the study. Similarly, the number of control patients who remained alive after 2 and 3 years was significantly ($p < 0.01$) less than their corresponding number a year earlier. This significance in observed differences of survival was lost at later time periods in the study (table 3). At the end of each of the first 5 years of the study, the number of patients remaining alive in each of the allopurinol and DMSO groups was similar but significantly ($p < 0.01$) larger than their corresponding control number (table 3).

Death was due to disease recurrence in 49 of 55 patients (89%) in the control group, in 35 of 51 patients (68.6%) in the allopurinol group and in 36 of 54 patients (66.7%) in the DMSO group. Survivor functions were estimated for the three study groups, and the differences between those for the control and allopurinol or DMSO groups were significant ($p < 0.01$). There was, however, no significant difference between the survivor functions for the allopurinol and DMSO groups.

A series of Cox proportional hazard models was fitted using, as covariates, all factors other than treatment to acquire a group of patients and postoperative factors that independently and significantly affect survival. Treatment with allopurinol and DMSO was then added as separate covariates. This showed that age over 70 years, the male sex, decreasing duration of symptoms, emergency presentation with vomiting and/or acute gastro-intestinal haemorrhage, blood transfusions immediately before, during or just after surgery and tumour dedifferentiation all had a significantly ($p < 0.001$) detrimental effect on survival at the 5% level. When these and all the non-significant variables (table 1) were allowed for, treatment with allopurinol or DMSO continued to exert a significant survival advantage ($p < 0.01$).

The influence of method of analysis on survival was studied. Intention-to-treat analyses were carried out to determine what might have happened if all patients had been evaluable or had died of cancer-related causes. This required postulating that some patients would have survived and others would have died at various time periods. When all the deaths excluded from the study (the postoperative cases and those who died from other than cancer-related causes) were assumed to have been cancer related, both allopurinol and DMSO continued to offer a survival advantage ($p < 0.05$). This advantage was maintained when only the control deaths were assumed to have been either cancer related ($p < 0.01$) or non-cancer related ($p < 0.05$). When all the patients who were excluded while still alive were assumed to have died

**Table 3.** Patient survival

| Time years | Control | | Allopurinol | | DMSO | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| 0 | 55 | 100 | 51 | 100 | 54 | 100 |
| 1 | 33 | 60 | 41 | 80.4 | 44 | 81.5 |
| 2 | 22 | 40 | 32 | 62.8 | 33 | 61.1 |
| 3 | 15 | 27.3 | 24 | 47.1 | 26 | 48.2 |
| 4 | 11 | 20 | 21 | 41.2 | 22 | 40.7 |
| 5 | 6 | 11 | 16 | 31.4 | 18 | 33.3 |

n = Number of patients alive.

during the study because of their gastric cancer, both allopurinol and DMSO continued to offer a survival advantage ($p < 0.05$). This advantage was maintained when only the patients excluded from the control group were assumed to have died because of their gastric cancer during the study period ($p < 0.01$) but lost when the assumption was that only the patients excluded from the allopurinol or DMSO groups died because of their gastric cancer during the same period.

## Discussion

The variables considered to be directly implicated in influencing the prognosis of patients with gastric cancer have been critically assessed. Maruyama [2] analysed 25 variables in patients with this cancer by multivariate analysis and identified the following factors to be especially important: depth of invasion, lymph node metastases, cancer type, location and histologic character. In the studies of Curtis et al. [14], 11 variables were analysed, and of these the depth of invasion, lymph node metastases and distant metastases were most significant. On the other hand, the multivariate analysis studies of Nakazato et al. [15] identified serosal involvement, lymph node metastases and distant metastases to be prognostically most important in gastric cancer. It, thus, appears that of the many factors relevant to survival after curative gastrectomy, the most important are the presence of serosal invasion, lymph node metastases with invasion of the perinodal fatty tissue and peritoneal dissemination, while hepatic metastasis is irrelevant [2, 7].

In patients with serosal invasion survival is lower in those who have peritoneal dissemination than in those without it [7]. This dissemination is largely produced by cancer infiltration from the serosa leading to free cancer cells within the peritoneal cavity and by invasion of the perinodal fatty tissues by the cancer cells that have metastasized into regional lymph nodes [7]. It, thus, follows that having carried out a gastrectomy for cancer with serosal invasion, an attack on the lymph nodes and peritoneal free cancer cells may contribute to prolonging survival. However, in relation to this point adjuvant chemotherapy in gastric cancer has failed to keep up to expectations [8], and the free cancer cells in the peritoneal cavity of patients with this cancer may retain their viability even after intraperitoneal mitomycin C [16]. With these facts and the knowledge that radiotherapy has only influenced survival when applied intra-operatively for locally advanced disease [9], the search continues for more effective, yet safe, carcinostatic treatments for the prevention of intraperitoneal dissemination of gastric cancer.

The present study was, therefore, conducted on gastric cancer patients with serosal invasion and metastases to the surrounding lymph nodes, who had no free cancer cells in their peritoneal cavity, because following gastrectomy they remain at risk of developing peritoneal recurrence and compromising their survival [7]. Such patients may, thus, be a valuable means for studying any influence scavengers of oxygen-derived free radicals might have on the survival of gastric cancer patients. The poor prognosis of patients with advanced gastric cancer might overshadow any effects afforded by radical scavengers on the rate of survival and this rate might not be influenced in patients with early gastric cancer where 90% or more have a 5-year survival rate [5, 6].

No general agreement seems to have been reached on the concept of curative resection. Soga et al. [17] identified curative resection on the basis of the following conditions: no grossly visible tumour left behind, histologic confirmation that resection margins (within 5 mm from resection lines) are free from can-

cer invasion and exclusion of any cases with remote cancer involvement although successfully removed. These authors argue that such a concept follows along the lines of the definition of curability widely employed in Japan but occasionally results in cases which actually belong to the non-curative group since there is a possibility of residual neoplastic tissue at the histologic level being left behind [17]. Consequently, the term 'potentially curative gastrectomy' was employed in this study to encompass the objective of the surgical approach at the time of the operation while accounting for the possibility of residual disease being left behind perhaps in the lymph nodes.

DMSO and allopurinol scavenge hydroxyl radicals [11, 12], and the latter agent also inhibits the enzyme xanthine oxidase which is responsible for the formation of superoxide radicals. These agents were equally effective in incurring a significant survival advantage in patients with carcinoma of the stomach over 5 years (table 3). The similarity in efficacy between allopurinol and DMSO (table 3) and the fact that the only action they share is scavenging free radicals suggest that the activities attributed to them in the present study were achieved by this scavenging. The knowledge that oxygen-derived free radicals are directly responsible for producing injury and damage of normal tissues [10–12] suggests that the tissue destruction associated with malignancy is caused by these radicals. It follows that oxygen-derived free radicals are implicated in the mechanism of gastric cancer and mediate its aggressiveness by producing the tissue damage which allows it to spread. Scavenging oxyradicals impairs this spread by sustaining the integrity of biological tissues, thus incurring a significant survival advantage. This advantage has also been noted in patients bearing colonic carcinoma treated with the same radical scavengers used in this study [18].

The survival rates noted in the present study (table 3) are similar to those reported by others [7], an observation which excludes the possibility that the survival advantage afforded by the radical scavengers might have been an experimental error or occurring in a heterogeneous group of patients of abnormally low survival. This investigation excluded patients with risk factors, those with a history of previous malignancy, those having synchronous or developing metachronous tumours or those dying from non-cancer-related causes so that as near a cancer-specific survival as possible, without the influence of any aggravating factors, could be calculated. Consequently, the survival advantages provided by removing oxyradicals were achieved by acting on cancer-related mechanisms rather than on non-cancer-related factors of a possible bearing on survival. Over the 5-year period of study, all patients who developed tumour recurrence subsequently died of their disease. The pattern of recurrence was similar in each of the three groups with peritoneal dissemination being the commonest. The use of computed tomography might have strengthened the study in terms of detection of distant tumour recurrences.

Although DMSO can be smelt in the breath, this was never a significant inconvenience to any patient. Furthermore, it could not be seen as a source of bias in favour of any group, since the major parameters of assessment were objective ones.


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