HIGH-DOSE MUSTINE THERAPY FOR BRONCHIAL CARCINOMA

BY

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As bronchial carcinoma becomes an increasingly common disease, while remaining largely incurable by surgery, so the need grows for effective methods of palliation. In this field the results of radiation therapy are disappointing and chemotherapy is even less satisfactory. Of the many anti-tumour drugs that have been used so far none has proved superior to mustine hydrochloride (nitrogen mustard; HN₂; methyl-bis (β -chloroethyl) amine) (Galton, 1958; Karnofsky, 1959). Cyclophosphamide is the most recent drug to be tried, but, although it has the advantage of oral administration, initial reports suggest it is relatively ineffective for this type of carcinoma (Anders and Kemp, 1961). The therapeutic dose of mustine, which is limited by its harmful effects on the bone-marrow, is generally taken to be 0.4 mg./kg. body weight (Goodman and Gilman, 1955), and this has been used in most previous trials. However, this somewhat cautious dose is but mildly damaging to both bone-marrow and tumour, and dissatisfaction with its results has led to a trial of more drastic therapy.

Assuming that the damage to a tumour increases with the quantity of drug delivered to it, then chemotherapy should be the most radical the patient can reasonably tolerate, provided the treatment is not more unpleasant than the disease. The single injection LD₅₀ for man being 1 mg./kg. body weight of mustine (Karnofsky, 1959) a divided dose of 0.8–1 mg./kg. was estimated to be maximal within the limits of toxicity. The following report describes the therapeutic and toxic effects of this high dose on 32 patients with advanced bronchial carcinoma.

Material and Methods

There were 26 males and six females in this series and their ages ranged from 36 to 73, 90% being in the fifth and sixth decades. In all cases the carcinoma was inoperable and the diagnosis had been proved histologically. The cell type was poorly differentiated in 15, anaplastic (oat cell) in 12, and squamous in five.

Every patient treated had severe symptoms and the majority were unsuitable for radiation therapy because of either widely disseminated disease or poor general condition. Leucopenia and thrombocytopenia (but not anaemia) were contraindications to treatment, and patients with appreciable haemoptysis were excluded.

The total dose of mustine was 1 mg./kg. body weight for the first 17 patients in the series and 0.8 mg./kg. for the subsequent 15. The course was divided into three equal injections given on consecutive evenings. The injections were given into an arm vein except when there was obstruction to the superior vena cava, in which case an infusion was set up via a "polythene" catheter into a large leg vein and the mustine was injected into the drip-set tubing.

Premedication with chlorpromazine 50 mg. and promethazine hydrochloride 50 mg. was given half an hour before each injection, and chlorpromazine was continued daily for as long as an anti-emetic was needed. To

minimize the risk of infection during the period of leucopenia each patient was treated in a single room, but strict isolation measures were not enforced. Prophylactic antibiotics were not used, but at the first sign of infection, most often a fever, tetracycline was prescribed. A haemoglobin of below 55% was usually an indication for blood transfusion. A total of 16 patients received antibiotics and seven were given blood transfusions. Sedatives, hypnotics, and analgesics were prescribed as required.

Results

The results of treatment were assessed in terms of subjective improvement, objective signs of tumour regression, and side-effects. By subjective improvement was meant relief of at least the main symptom; in the case of pain complete freedom from analgesics. Evidence of tumour regression included radiological appearances showing re-aeration of collapsed lung and reduction in size of enlarged glands, disappearance of the clinical signs of superior vena caval obstruction, and diminution of palpable metastases.

The results were analysed according to the following categories, which are modified from a scheme of assessment suggested by Karnofsky (1961): (A) subjective and objective improvement maintained for over four weeks; (B) subjective improvement maintained for over four weeks, but no objective changes; (C) subjective or objective improvement lasting less than four weeks; (O) no favourable subjective or objective changes. In Table I the results of treatment are analysed according to tumour histology.

TABLE I.—Response of 32 Patients to Mustine (0.8–1 mg./kg. Body Weight)

Tumour Histology	Category of Response to Treatment			
	A	B	C	O
Squamous	3	0	0	2
Poorly differentiated	7	2	3	4
Anaplastic	4	2	4	1
Total	14	4	7	7

A response to treatment which was maintained for less than four weeks was not considered to be of practical benefit to the patient. Thus only categories A and B could be regarded as satisfactory, and all patients in these two categories were rendered fit enough to be discharged from hospital.

Of 32 patients treated 18 responded with symptomatic improvement of significant duration and all except four of these also showed signs of tumour regression. Satisfactory results were achieved in patients with squamous-cell, poorly differentiated, and anaplastic carcinoma. Of the eight cases of superior mediastinal compression, six were improved. In general the remissions lasted between four and eight weeks, and in only three patients was the improvement maintained for longer than three months. One patient received two courses of treatment with benefit only from the first course, and another was given three courses, each one producing a remission of six weeks.

Survival time was not taken as a measure of palliation, but five of the 32 patients were still alive six months after the start of treatment.

Side-effects

Anorexia and nausea invariably followed the mustine injections and vomiting was common; the reactions

varied greatly from patient to patient and rarely lasted longer than three days. A mild chemical thrombophlebitis at the site of injection occurred in nearly half the cases. The treatment was not complicated by diarrhoea or damage to the central nervous system. In general the higher dose of mustine caused little more discomfort to the patients than is usual with the conventional dose.

The most serious side-effects resulted from bone-marrow depression. The leucocyte and platelet counts in the peripheral blood started to fall at the end of the first week after treatment and reached the lowest levels between the fourteenth and eighteenth days. The minimum leucocyte counts ranged from 2,800 to 60/c.mm., with values below 1,000 in half the cases; the minimal platelet counts ranged from 87,000 to 4,000/c.mm., with values below 40,000 in 60% of cases. Both leucocyte and platelet counts invariably returned to normal before the end of the fourth week. During the same period a fall of haemoglobin concentration of between 10 and 40% occurred in 80% of cases, followed by a gradual rise to pretreatment levels.

Despite the frequency of severe thrombocytopenia, haemorrhage was surprisingly uncommon; transient purpura occurred in several patients and epistaxes in five. However, two patients died with massive haemoptysis, and these deaths must be counted as due to mustine. During the period of severe leucopenia acquired infection was treated with antibiotics, but three patients died of pneumonia, with leucocyte counts below 1,000/c.mm. Thus in five of the 32 patients death was hastened by the mustine. Three of these received 0.8 mg./kg. body weight and two received 1 mg./kg.; all were over the age of 64.

Discussion

Good palliative treatment for cancer should be easily administered, rapid in action, predictable in its effect, and not unpleasant for the patient. In bronchial carcinoma no current method approaches this ideal. The therapeutic effects of mustine appear within two to three days of treatment, but in the present series only 18 of the 32 patients benefited from it. The drug is easily administered, but there are unpleasant side-effects which, being short-lived, are readily forgotten by the patients who improve but are less acceptable for those who do not.

In Table II are summarized the results of the largest previous trials of mustine therapy for bronchial carcinoma. Unfortunately there has been no uniform definition of terms, so that a valid comparison with the results of the present method is impossible. A wide variation of response to the same dose of mustine has

been recorded, with subjective benefit ranging from 41 to 75% and objective improvement from 18 to 54%. Since methods of patient-selection are unlikely to differ much from one series to another the discrepancy in results must largely be due to different criteria of assessment, particularly with regard to the minimum period of improvement.

There is little reason to believe that mustine therapy appreciably prolongs life (Wolf *et al.*, 1960) except in cases of superior mediastinal compression. Thus the success of treatment must be assessed by symptomatic improvement, an effect which cannot be measured objectively and is liable to observer bias. For this reason more reliance should be placed on symptomatic improvement accompanied by objective changes (category A) than in their absence (category B). However, objective signs of tumour regression are not by themselves a reliable index of palliative success, for they can occur without parallel symptomatic improvement.

In five of the 32 patients in this series death was hastened by the treatment. A mortality rate of 16% might be regarded as prohibitive, but, considering the extremely poor prognosis of these patients and that 63% of those who survived benefited from the treatment, the risk seemed to be a reasonable one. In fact, the six months' survival rate in this series was 16%, which is identical to that in a previous series of 87 patients treated at Sully Hospital with conventional doses of mustine.

There is some uncertainty about the relation between tumour histology and response to chemotherapy. Some authors have reported the best results with anaplastic carcinoma (Roswit and Kaplan, 1951; Levine and Weisberger, 1955), others with squamous-cell carcinoma (Hurley *et al.*, 1961), while a third group found no correlation with histology (Ayers, 1951). In this series, limited by the small proportion of squamous-cell carcinoma, there was little difference in behaviour between the cell types. This lack of specificity of response contributes to the difficulty in predicting which patients are likely to do well and so of improving case-selection. From present experience it seems that in general those in an extreme cachectic state tolerate the treatment poorly and where there are large tumour masses the therapeutic effect is small. In such patients the use of mustine is not justified. However, in cases with more limited disease causing atelectasis or superior mediastinal compression the response is better, for in these a relatively slight reduction in tumour size can achieve a large therapeutic effect.

A method of palliative treatment with a 56% success rate and an average remission time of only a few weeks can hardly be claimed as satisfactory, although at present there seems to be no more effective form of chemotherapy for advanced lung cancer. Theoretically the effectiveness of mustine might be improved by increasing the tumour dose still further. This can be achieved without causing fatal damage to the bone-marrow by excluding the diseased lung from the systemic circulation and perfusing it with the chemotherapeutic agent (Creech *et al.*, 1959). This is a complicated procedure involving two extracorporeal circuits and is unsuitable for the treatment of disseminated cancer. Another approach is to use high systemic doses of drugs in conjunction with a form of partial bone-marrow protection. Four patients in the

TABLE II.—Summary of Previous Trials of Mustine for Bronchial Carcinoma

Authors	No. of Patients Treated	Percentage Subjective Improvement	Percentage Objective Improvement	Total Dose of HN2 in mg. kg. Body Weight
Karnofsky <i>et al.</i> (1948)	35	74	49	0.4
Lynch <i>et al.</i> (1950)	60	69	54	0.4
Ayers (1951)	68	41	—	0.4
Roswit and Kaplan (1951)	40	75	48	0.4
Raphael and Reilly (1954)	56	46	20	0.4
Levine and Weisberger (1955)	32	41	22	0.4-1.5
Hatch <i>et al.</i> (1956)	169	46	20	0.4
Bell (1962)	62	60	18	0.4

present series had sphygmomanometer cuffs inflated around the upper thighs in an attempt to protect the bone-marrow of the lower limbs during the short period of mustine activity. This method failed, but successful bone-marrow protection has apparently been achieved by more complex means such as occlusion of the abdominal aorta with an intra-aortic balloon catheter (Miller and Lawrence, 1961) or external abdominal compression (Duff *et al.*, 1961) or by differential perfusion hypothermia of the lower limbs and pelvis (Lee *et al.*, 1962). Yet even with successful bone-marrow protection the dose of drug is still limited by damage to other vital tissues. Thus mustine in high concentrations may cause serious harm to the central nervous system and intestinal mucosa.

Satisfactory results in lung cancer chemotherapy will probably have to await the discovery of new drugs which are less damaging to normally dividing tissues. Meanwhile in carefully selected cases the best palliation can be achieved with the drugs at present available if they are given in maximal doses.

Summary

Thirty-two patients with advanced bronchial carcinoma were treated with a maximal sublethal dose of mustine (nitrogen mustard). The therapeutic and toxic effects are described and the method is discussed in relation to other chemotherapeutic techniques. In

view of the striking powers of recovery of bone-marrow after damage by mustine, it is suggested that the currently accepted therapeutic dose is unduly small.

I wish to thank Dr. L. R. West, under whose care these patients were admitted, for his interest and advice.

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Preliminary Communications

Combined Nitrogen Mustard and Hyperbaric Oxygen Therapy in Advanced Malignant Disease

The belief that tumour cells are more susceptible to damage by ionizing irradiation and certain chemicals when the oxygen tension of tissues is increased led us to study the effects of a cytotoxic drug given to patients with advanced malignant disease under conditions in which the oxygen tension of all body tissues is greatly increased.

Methods.—The patients, who were not premedicated, were taken into a specially designed pressure-chamber, details of which have already been published (Illingworth *et al.*, 1961). While the patient inhaled oxygen continuously the pressure was increased to and maintained at two atmospheres (absolute). After 15 minutes at full pressure a single dose of nitrogen mustard, 0.5 or 0.6 mg./kg. body weight, was given into a fast-running intravenous saline infusion; 20 to 30 minutes later the pressure was reduced to atmospheric, the oxygen inhalation was discontinued, and the patient was returned to the wards.

CASE REPORTS

Case 1.—A man aged 50 had had a total gastrectomy with oesophago-jejunal anastomosis, splenectomy, and partial pancreatectomy for carcinoma of the stomach in 1955. He remained well on vitamin-B₁₂ therapy until 1960, when he had a myocardial infarct. Although symptom-free, secondary deposits were seen on chest x-ray films at this time. He was readmitted because of pleuritic chest pain and general deterioration nine months later. Treatment with 26 mg. of nitrogen mustard (0.6 mg./kg. body weight) in the pressure-chamber did not give any subjective benefit

and there was no change in the radiological appearances of the chest lesions on the 3rd, 9th, and 18th days after treatment. Marrow damage was manifest by a fall of previously normal peripheral blood values to Hb 55% and W.B.C. 500/c.mm. on the 10th day after treatment, but there was spontaneous and complete restoration to normal before death 23 days after treatment. Microscopical examination of the pulmonary lesions obtained at necropsy showed a well-differentiated mucin-secreting adenocarcinoma of the stomach morphologically identical to the primary tumour: there was no evidence of damage to the specimens of tumour examined.

Case 2.—A man aged 39 had had a total gastrectomy with oesophago-jejunal anastomosis for carcinoma of the stomach in 1959. Dysphagia began one year after operation, and although no abnormality was seen on oesophagoscopy there was radiological evidence of obstruction at the anastomosis. Bouginage afforded temporary relief. A nodule appeared in the abdominal wound and part was excised: microscopy showed secondary tumour. Treatment with 27 mg. of nitrogen mustard (0.5 mg./kg. body weight) in the pressure-chamber gave marked subjective relief from dysphagia, but there was no histological evidence of damage to the remainder of the tumour nodule, which was excised on the 7th day after treatment. Dysphagia recurred, and a second treatment with 27 mg. of nitrogen mustard (0.5 mg./kg. body weight) was given in the pressure-chamber 31 days after the first treatment. Again there was brief subjective benefit but no objective evidence of improvement, and he continued to deteriorate slowly, dying four months after the initial treatment. The peripheral blood values did not fall after either treatment. Microscopical examination of the primary tumour, the secondary lesions in the abdominal wound, and tumour tissue within the abdomen obtained at necropsy did not reveal any differences between the samples, all of which were those of a poorly differentiated mucin-secreting adenocarcinoma of the stomach.

Case 3.—A woman aged 52 was admitted to hospital in a confused state as an emergency case. The main features on examination were dysphasia, right facial weakness, papilloedema, hyperreflexia, and extensor plantar responses. X-ray examination of the skull showed no abnormality, but a right-sided hilar mass was seen on the chest film. E.E.G.