Prednisolone and Mustine in Prevention of Tumour Swelling during Pulmonary Irradiation

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Summary

Ventilatory function declines during the early stages of irradiation for bronchial carcinoma. This decline is potentially dangerous if the tumour narrows the trachea or both main bronchi. The protective effect of preliminary treatment with prednisolone or mustine before irradiation was studied in 88 patients by serial estimations of forced expiratory volume and forced vital capacity. Twenty-three patients received prednisolone by mouth, 24 had mustine intravenously, and 41 had no preliminary treatment. Both prednisolone and mustine prevented a significant decline in ventilatory function due to tumour swelling, prednisolone being marginally superior. It is concluded that all patients at risk should be treated with oral prednisolone, 20 mg daily, for one day before and two days after the first fraction of irradiation.

Introduction

For some years we have had the impression that patients with tumours extensively involving the trachea and major bronchi are liable to develop severe respiratory distress, or even to die from asphyxia, during the early stages of a course of treatment with deep *x* rays. This phenomenon was recently investigated in a prospective study of 42 patients by means of serial estimations of ventilatory function during irradiation for bronchial carcinoma (Cameron *et al.*, 1969).

All patients with tumour or metastatic lymph nodes involving the trachea, main carina, or both main bronchi showed a significant decline in the forced expiratory volume in one second (FEV_1) after two to four treatment fractions. This decline was temporary, and had been reversed by the end of the first week of therapy, presumably as a result of tumour shrinkage caused by cell death as irradiation continued. A similar but less pronounced decline was observed in most patients with tumours involving a main or lobar bronchus. It was suggested that the initial reduction in FEV_1 was due to intracellular and extracellular oedema with resultant tumour swelling. Although temporary, this tumour swelling in the early stages of irradiation was considered to be potentially dangerous, particularly when the tumour involved the tracheal bifurcation or a main or lobar bronchus in patients whose pulmonary function was already seriously compromised by chronic bronchitis and emphysema. It was postulated that preliminary treatment with either corticosteroids or mustine hydrochloride might prevent tumour swelling and consequent aggravation of airway obstruction. We now report a new study designed to test this hypothesis.

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Case Selection

All the 88 patients included in the study had partial obstruction of a lobar or larger bronchus. They received either radical irradiation with 5,000 rads given in 20 fractions over four weeks or palliative irradiation with 2,000 rads given in six fractions in one week. Forty-seven patients were divided at random into two groups for preliminary treatment with mustine hydrochloride or prednisolone, and 41 patients included in the previous study (Cameron *et al.*, 1969) formed the third (control) group.

The *Mustine Group* (*M*) consisted of 24 patients who received an intravenous infusion of mustine hydrochloride (0·4 mg/kg body weight) 48 hours before the start of irradiation. The *Prednisolone Group* (*P*) consisted of 23 patients who were treated with prednisolone in a dose of 20 mg/day by mouth for 24 hours before and 48 hours after the start of irradiation. The *Control Group* (*C*) consisted of 41 patients included in our previous report who received no preliminary drug treatment before irradiation.

The patients in each group were divided into two subgroups on the basis of the bronchoscopic findings. *Subgroup 1* consisted of patients in whom the tumour involved the trachea or both main bronchi and *Subgroup 2* of patients in whom the tumour involved a main or lobar bronchus.

All patients were selected and classified in the same way as those reported in the earlier study. The numbers in the various groups and subgroups and their pretreatment status are shown in Table I.

TABLE I—*Pretreatment Status of 47 Patients Studied, with Details of 41 Control Patients*

Subgroup	Total	Age (Years)		Sex		FEV_1 before any treatment (ml)	
		Range	Mean	M.	F.	Range	Mean
M1 ..	10	40-69	59	9	1	700-2,700	1,377
M2 ..	14	54-82	63	13	1	600-2,500	1,285
P1 ..	8	56-84	65	6	2	800-2,400	1,516
P2 ..	15	51-74	64	11	4	440-1,950	1,210
C1 ..	14	38-77	57	12	2	800-3,100	1,430
C2 ..	27	14-77	61	25	2	780-2,420	1,485

Method of Investigation

During the first three days in hospital, before treatment was started, five separate measurements (each the highest of three recordings) were made of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) with a Vitalograph dry spirometer. The same measurements were made twice daily (at 9 a.m. and 6 p.m.) after the intravenous infusion of mustine hydrochloride, or following the start of oral treatment with prednisolone. These measurements were then repeated twice daily during the first seven days of irradiation treatment.

Results

Control Group (*C1*/*C2*).—The results in this group are those reported in our previous paper (Cameron *et al.*, 1969). In Subgroup C1 there was a significant fall in FEV_1 in all 14 patients during the first three days of irradiation, followed by a steady

TABLE II—*Forced Expiratory Volume and Indices of Decline before Treatment with Mustine or Prednisolone and during Subsequent Irradiation*

Subgroup	FEV_1 before Irradiation				FEV_1 during 1st Week of Irradiation				
	Before Drug Treatment		After Drug Treatment		Mean of Lowest 2 FEV_1 Readings	Index of Decline I_1		Index of Decline I_2	
	Range	Average	Range	Average		Range	Average	Range	Average
M1	700/2,700	1,377	630/2,510	1,352	1,210	−0·34/4·23	1·99	−0·52/4·73	1·85
M2	600/2,500	1,285	560/2,400	1,220	1,187	0·50/3·47	1·83	−2·44/3·47	1·00*
P1	800/2,400	1,516	900/2,450	1,605	1,486	−0·79/2·23	0·92	−0·57/2·02	0·77
P2	440/1,950	1,210	450/1,900	1,217	1,140	0·08/3·73	1·49	−0·50/3·73	1·35
C1	800/3,100	1,430			1,208	1·41/10·98	5·21		
C2	780/2,420	1,485			1,286	0·20/9·70	2·94		

*The low value of 1·00 is due to two patients in whom the FEV_1 declined sharply after mustine infusion before irradiation. If these patients are excluded the average I_2 for the 12 M2 patients is 1·48.

improvement. In Subgroup C2 22 of the 27 patients showed a significant reduction in FEV_1 during the first four days of irradiation. The decline in FEV_1 in both subgroups was significantly greater ($P < 0·01$) than that observed in patients who received irradiation to peripheral bronchial tumours or to extrathoracic tumours. The average and range of FEV_1 before irradiation, with the mean of the lowest two readings during the first week of irradiation, are shown in Table II.

Mustine Group (M1/M2).—The average and range of the five pretreatment readings of FEV_1 and of the four readings after mustine, and the mean of the lowest two recordings of FEV_1 during the first week of irradiation, are shown in Table II. Intravenous infusion of mustine hydrochloride two days before the first fraction of irradiation was followed by a slight fall in FEV_1 in some patients, but this was not pronounced in any individual patient. There was no significant decline in serial readings during the first week of irradiation in any of the 10 patients with central tumours (Subgroup M1) or of the 14 patients with more peripheral lesions (Subgroup M2).

Prednisolone Group (P1/P2).—The results for this group are also shown in Table II. There was no early decline in FEV_1 in eight patients with central tumours (Subgroup P1) or in 15 patients with more peripheral tumours (Subgroup P2). Indeed, preliminary treatment with prednisolone was associated with a slight but significant improvement in FEV_1 over the baseline readings. Subsequent irradiation did not cause a significant fall in FEV_1 in any patient, and in most patients the preirradiation improvement was maintained.

Notes on Statistical Analysis

Effect of Preliminary Drug Treatment Itself.—The average of the five readings of FEV_1 for each patient after admission was compared with the average FEV_1 during drug treatment. The statistical analysis of these data (Table III) confirmed that preliminary treatment with prednisolone in patients with central tumours produced a slight but significant improvement in FEV_1, while patients treated with mustine showed a slight decline.

Comparison of Mustine and Prednisolone in Respect of Decline in FEV_1 after Start of Irradiation.—The comparison was complicated by the compounding of drug and irradiation effects.

TABLE III—*Group Average FEV_1 before Treatment with Prednisolone or Mustine Compared with Average FEV_1 during Drug Treatment but before Irradiation*

Subgroup	Before Drug Treatment	During Drug Treatment	Level of Significance (Wilcoxon's Test)	Conclusion
P1	1,516·9	1,605·4	$P < 0·05$	Significant increase
P2	1,208·4	1,216·7	$P > 0·05$	Not significant
M1	1,378·6	1,351·4	$P > 0·05$	Not significant
M2	1,282·6	1,220·6	$P < 0·01$	Significant decline

Two separate analyses were therefore made, each using an "index of decline" for purposes of comparison (Table II; Figs. 1 and 2). The first was:

$$\text{1st index of decline } (I_1) = \frac{\text{mean } FEV_1 \text{ before any treatment} - X}{\text{pooled S.D. of group before treatment}}$$

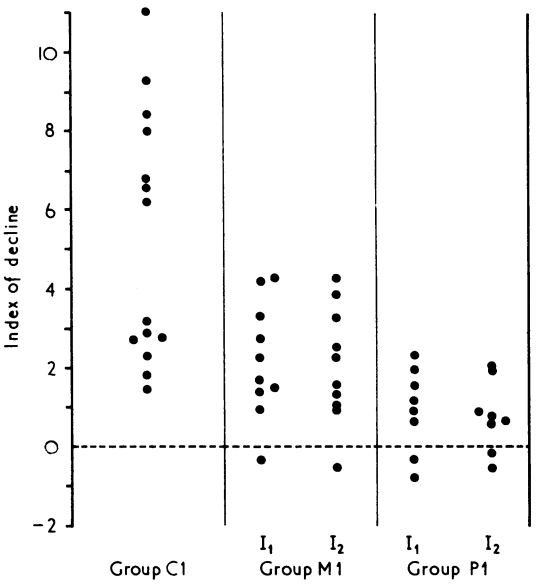

FIG. 1—Individual indices of decline in patients with central bronchial tumours (Subgroups 1).

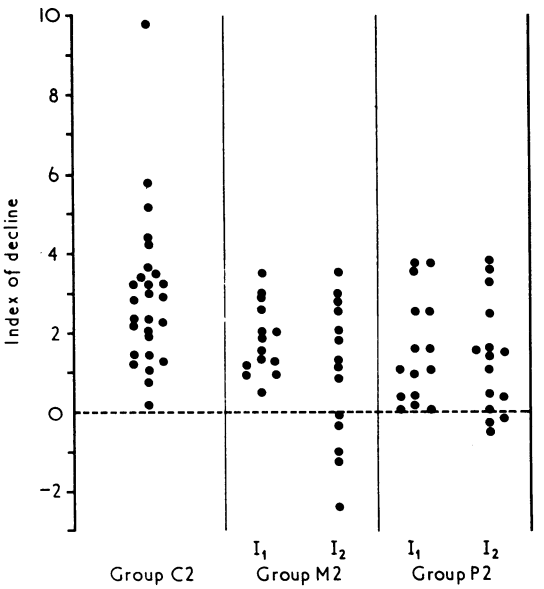

FIG. 2—Individual indices of decline in patients with lobar bronchial tumours (Subgroups 2).

TABLE IV—*Comparison of Combined Prednisolone and Mustine Subgroups with Control Subgroups, using Indices of Decline*

Subgroup	Sample Size	Average I_1	Level of Significance	Average I_2	Level of Significance
P1 and M1	18	1·51		1·37	
C1	14	5·21		5·21	
		difference = 3·70	P < 0·01	difference = 3·84	P < 0·01
P2 and M2	29	1·65		1·18	
C2	27	2·94		2·94	
		difference = 1·29	P < 0·05	difference = 1·76	P < 0·05

where X = mean of lowest two FEV_1 readings within the 10 which followed the start of drug treatment (this included some readings after irradiation). There was *no* significant difference in the value of I_1 in any of the treatment comparisons: (*a*) mustine group, comparing M1 and M2; (*b*) prednisolone group, comparing P1 and P2; and (*c*) an overall analysis of variance on the four subgroups. The same conclusions were drawn when the second index of decline was used:

$$\text{2nd index of decline } (I_2) = \frac{\text{average } FEV_1 \text{ before any treatment} - Y}{\text{pooled S.D. of group before treatment}}$$

where Y = mean of lowest two FEV_1 readings within the 10 which followed the start of irradiation (this excluded any readings before irradiation). While no significant difference was shown between the four subgroups who received preliminary drug treatment, the indices of decline were slightly greater in patients receiving mustine than in those treated with prednisolone.

Comparison of Combined Mustine and Prednisolone Pretreatment Groups with Control Group.—The numbers in each subgroup receiving prednisolone or mustine were small, and since there was no significant difference between these subgroups they were combined for comparison with the control patients. When indices of decline were used, the control group registered a greater fall in FEV_1 during irradiation than did the combined mustine and prednisolone groups (Table IV), and these differences were significant at the 1% level when patients with central tumours (Subgroups 1) were compared.

Validity of FEV_1 as an Index of Airway Obstruction.—In order to establish whether a decline in FEV_1 represented a true reduction in bronchial air flow, or merely reflected a general reduction in vital capacity during the early stages of treatment, a study of the changes in FEV_1/FVC ratio (usually regarded as a reliable index of airway obstruction) was undertaken. The difference between mean pretreatment FEV_1/FVC and the mean of the lowest FEV_1/FVC during the first week of irradiation was calculated (denoted by D). The value of D in Subgroups C1, C2, M1, M2, P1, and P2 was tested, and the differences between C1 and C2, M1 and M2, P1 and P2, M1 and P1, and M2 and P2 were found not to be significant, but when M1 or P1 was compared with C1, and M2 or P2 with C2, significant differences were observed ($P < 0·05$). Since these statistical conclusions corresponded with those drawn from indices of decline based on FEV_1, it was assumed that the latter accurately reflected changes in the degree of airway obstruction.

Discussion

Most of the previous physiological studies on the effects of deep *x* rays in bronchial carcinoma have been concerned with disturbances of function caused by damage to the lung parenchyma (Whitfield *et al.*, 1956; Deeley, 1960; Evans, 1960; Emirgil and Heinemann, 1961; Hoffbrand *et al.*, 1965), and little attention has been paid to the effects of irradiation on the tumour itself. As has been shown by Cameron *et al.* (1969), these effects occur during the first 48 hours of treatment and are not delayed for several weeks, as in the case of irradiation damage to lung tissue. When a bronchial carcinoma is irradiated there is an initial phase of tumour swelling, which increases the degree of bronchial obstruction. If the tumour is situated in the region of the tracheal bifurcation the airway may become almost completely obstructed, and death from asphyxia may result.

It has been shown in the study reported in this paper that preliminary treatment with either intravenous mustine or oral prednisolone can prevent initial tumour swelling during irradiation. Prednisolone is marginally superior to mustine in this respect because it produces a slight, but significant, immediate increase in FEV_1 which is not reversed by subsequent irradiation. A similar improvement is not observed with mustine, which has the additional disadvantage of being much more toxic and difficult to administer.

It is concluded that all patients with tumours involving the trachea or major bronchi who are being treated with deep *x* rays should be protected from the risks of initial tumour swelling by preliminary treatment with prednisolone by mouth in a dose of 20 mg/day for 24 hours before and 48 hours after the start of irradiation. Such treatment given for only 72 hours is unlikely to accelerate tumour growth and may prevent unnecessary fatalities.

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