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Role of Pulmonary Function Tests in the Prevention of Bleomycin Pulmonary Toxicity during Chemotherapy for Metastatic Testicular Teratoma

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Abstract—*Thirty-eight men were treated for metastatic testicular teratoma with up to four courses of chemotherapy, each containing* 90 mg *bleomycin. Routine pulmonary function tests (PFTs) were performed before each course to assess their value in detecting bleomycin pulmonary toxicity. PFTs were repeated* 2–5 *yr after completion of chemotherapy in* 10 *disease-free survivors. Analysis of changes in individual PFT values showed a fall in the carbon monoxide diffusing capacity (DL_{CO}) after* 90 mg *bleomycin* ($P < 0.005$). *The DL_{CO} remained depressed with subsequent doses of bleomycin, but there was no further statistically significant fall. There was no significant change in any other PFT. Similarly, late PFT values showed no significant change. There was no correlation between changes in the visible extent of metastases as assessed from the chest radiograph and changes in serial PFTs. It is concluded that routine PFTs are unnecessary if the total bleomycin dose is* ≤ 360 mg, *unless there are particular risk factors. Late drug-induced pulmonary damage is unlikely to develop after treatment withdrawal.*

INTRODUCTION

BLEOMYCIN is a non-myelosuppressive polypeptide antibiotic cytotoxic agent. Its most important dose-limiting toxic effect is pulmonary fibrosis. Other toxic effects include fevers, cutaneous striae, alopecia and weight loss. In general, the incidence and severity of bleomycin pulmonary toxicity is related to the total dose of bleomycin administered. Most cases are associated with total doses > 500 mg [1].

Several studies have used pulmonary function tests (PFTs) to attempt to detect early pulmonary toxicity and hence to prevent severe toxicity by stopping bleomycin treatment in susceptible individuals. Most studies have been performed in heterogeneous groups of patients receiving bleomycin in various doses and by various schedules, making interpretation difficult [2–4].

Patients with metastatic testicular teratoma are a relatively homogenous group of previously healthy young men. Chemotherapeutic regimes using bleomycin with either vinblastine alone or vinblastine and *cis*-diamminedichloroplatinum are capable of inducing long-term complete remissions in 40–70% of cases [5, 6]. It is important, therefore, to avoid long-term toxicities in these 'cured' patients.

Routine serial PFTs require specialised staff and equipment and are time-consuming. They are justified if shown to detect early pulmonary toxicity and to enable avoidance of serious damage with currently used chemotherapy regimens.

The present study was designed to evaluate:

(a) Whether it is necessary to routinely perform serial PFTs in a group of patients being treated for metastatic testicular teratoma by combination chemotherapy including bleomycin at a total dose ≤ 360 mg.

(b) Whether one particular PFT can be selected as the most significant in the prediction of bleomycin pulmonary toxicity.

(c) Whether changes in PFTs can be correlated with changes in the visible extent of pulmonary metastases assessed from the chest radiograph.

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(d) Whether there is progressive damage with time in patients considered disease-free.

MATERIALS AND METHODS

Patients

Serial PFTs were performed in 38 men treated for metastatic testicular teratoma at the Christie Hospital, Manchester, from 1974 to 1978. Their mean age was 28.4 yr (range 15–51 yr). Table 2 summarises details of the extent of metastases before chemotherapy and the outcome of treatment. The staging system used was a modification of that described by Peckham *et al.* [7]. The median follow-up time is 3.5 yr (range 2–6 yr).

Three patients had had radiotherapy to a part of one lung before beginning chemotherapy. In each case, the irradiation was given by parallel opposed fields. The doses were 3000 cGy in 8 fractions in 11 days, 3750 cGy in 16 fractions in three weeks and 4000 cGy in 16 fractions in three weeks.

Pulmonary function

The PFTs performed were those commonly available in respiratory function laboratories comprising forced expiratory volume in one second (FEV_1), vital capacity (VC), residual volume (RV), total lung capacity (TLC) and single breath carbon monoxide diffusing capacity (DL_{CO} or transfer factor). RV and TLC were measured by closed-circuit spirometry and helium dilution. Two general points apply to all the tests. Firstly, lung function depends on age, size and sex, and normal values vary enormously. Secondly, there is a variation in the test results themselves because of intrinsic biological variability and variability of apparatus and of operator. Results are only considered abnormal if they are $>20\%$ higher or lower than predicted normal values.

For each patient, predicted normal values for each PFT were calculated. Preliminary PFTs were measured in all patients before the first chemotherapy course was administered. PFTs were repeated before each chemotherapy course.

Table 1. Histology

Histology	*No.*
Malignant teratoma intermediate (MTI)	14
Malignant teratoma undifferentiated (MTU)	19
Mixed seminoma/teratoma	5
Total	38

Table 2. Patient details

Presenting stage	No.	Mean time to first metastasis (months)	Sites of metastases at start of chemotherapy				Alive Disease free	Alive with disease	Disease death	Death of treatment effects
			Nodes	Lung	Liver	Brain				
1	16	8	8	11	0	1	9	1	4	2*
2	4	—	4	1	0	0	2	0	2	0
3	2	—	2	0	0	0	1	0	1	0
4	16	—	13	15	2	1	3	1	12	0
Totals	38		27	27	2	2	15	2	14	2

*Secondary to marrow supression.

In ten patients who are currently alive and disease-free PFTs have been repeated between two and five years after completion of chemotherapy.

A chest radiograph was taken before each chemotherapy course. The visible extent of pulmonary metastases has been classified as: absent, 1–9, 10–19, >20 metastases visible. Twenty-seven of the 38 men had pulmonary metastases at the beginning of chemotherapy and one additional patient had had pulmonary metastases which had completely responded to radiotherapy.

Treatment

Two chemotherapeutic regimens were used which are described in Table 3. Each regimen was given monthly to a total of four courses. Twenty patients received regimen 1 (vinblastine and bleomycin, 1974–1977), of whom three are currently alive and disease-free. Eighteen patients received regimen 2 (vinblastine, bleomycin and *cis*-diamminedichloroplatinum, 1976–1978), of whom 11 remain alive and disease-free.

It was decided to stop bleomycin in any patient whose clinical features or chest radiograph suggested toxicity or whose PFT results became abnormal, in particular if the DL_{CO} fell below an absolute level of 20 mg/ml/min. The latter occurred in two patients after 180 mg and 270 mg bleomycin respectively. The remaining 36 men all received four courses of chemotherapy, each containing 90 mg bleomycin (360 mg total dose). No patient received more than 360 mg bleomycin.

Table 3. Chemotherapy regimen

	Drug schedule	Interval (months)	No. of courses	No. treated	Current disease-free survivors
Regimen 1	Vinblastine 6 mg/m^2 i.v. days 1, 2 Bleomycin 15 mg i.m. 12-hourly, days 2, 3, 4	1	4	20	3 (15%)
Regimen 2	Vinblastine 6 mg/m^2 i.v. days 1, 2 Bleomycin 15 mg i.m. 12-hourly, days 2, 3, 4 *Cis*-diamminodichloroplatinum 20 mg/m^2 i.v. days 2,3,4,5,6	1	4 3 2	16 1 1	11 (61%)

Statistical analysis

Each PFT value was expressed as a percentage of the pretreatment value. Percentage changes in PFTs with increasing bleomycin dose were analysed by means of the Wilcoxon signed rank test and paired *t* variance. These non-parametric tests were used because the data did not seem to be normally distributed. The data is thus most appropriately illustrated by median values.

An attempt was made to correlated the visible extent of metastases on the chest radiograph with PFT values by linear regression.

RESULTS

No cases of bleomycin pulmonary toxicity were detected in the 38 men considered.

Table 4 shows the median PFT values related to bleomycin dose. Table 5 shows the median percentage changes in PFT values from pretreatment values related to bleomycin dose.

Table 4. Median PFT values related to bleomycin dose (with lower and upper quartile values and number of patients)*

PFT	Predicted	Preliminary	Following bleomycin 90 mg	180 mg	270 mg	360 mg (Late values)
FEV_1	4.2	4.2	4.3	4.3	4.4	4.7
(Litres)	3.9–4.3	3.5–4.8	3.5–5.0	3.6–4.9	3.6–4.9	3.6–5.2
	38	38	38	37	21	10
VC	5	5.2	5.4	5.3	5.3	5.6
(Litres)	4.7–5.2	4.6–5.7	4.6–5.9	4.5–5.8	4.7–5.7	4.8–6.7
	38	38	38	37	21	10
RV	1.9	2	1.9	1.9	1.9	1.9
(Litres)	1.8–2.0	1.7–2.3	1.5–2.2	1.5–2.4	1.3–2.2	1.6–2.7
	38	37	38	36	20	9
TLC	7	6.8	6.8	6.5	6.5	7.4
(Litres)	6.5–7.1	6.2–7.8	5.9–7.6	6.0–7.6	5.6–7.4	6.2–8.1
	38	37	38	36	20	9
DL_{CO}	34.2	28.2	24.5	24.5	26.5	28.5
(ml/min/mmHg)	23.2–40.2	23.5–33.0	21.0–29.0	20.0–30.0	22.5–29.3	26.5–31.5
	38	38	38	37	21	10

*Range excluding upper 25% and lower 25% values.

Table 5. Median percentile change in PFT values from preliminary values related to bleomycin dose (with lower and upper quartile values and number of patients)

P.F.T.	Preliminary	Following bleomycin 90 mg	180 mg	270 mg	360 mg (Late values)
FEV_1	100%	100.4%	101.8%	102.1%	97.7%
(Litres)		96.4–105.6%	95.7–105.5%	97.1–110%	95.6–87.8%
		38	37	21	10
VC					
(Litres)	100%	102.3%	100.1%	98.7%	99.1%
		94.6–107.6%	95.9–103.9%	92.6–105.4%	97.6–101.4%
		38	37	21	10
RV					
(Litres)	100%	96.7%	98.9%	100%	109.1%
		77.5–107.4%	77.5–120%	68.8–107%	90.7–116.5%
		38	36	20	9
TLC	100%	98.9%	98.9%	97.9%	98.4%
(Litres)		91.5–104%	90.6–106%	86.3–102.7%	94.9–106.4%
		38	36	20	9
DL_{CO}					
(ml/min/mmHg)	100%	94.6%	92.5%	87.9%	98.4%
		83.8–104.6%	78.8–101.7%	80–106.4%	90–105.6%
		38	37*	21*	10

*Significantly different ($P < 0.005$) from the 90 mg dose using the Wilcoxon matched pairs signed rank test and paired t variance.

In each case the lower and upper quartile values and the number of values available are quoted.

There was a statistically significant fall in the DL_{CO} value following 90 mg bleomycin ($P < 0.005$). The DL_{CO} values remained depressed with further bleomycin but there was no further significant fall. There was no statistically significant change in any other PFT related to increasing bleomycin dose. The values in the final column of Table 4 were measured 2–5 yr after completion of chemotherapy in 10 disease-free survivors. Analysis showed no evidence of late changes in PFT values.

Table 6 shows the response of pulmonary metastases to the two chemotherapy regimes used. A complete response means the disappearance of visible pulmonary metastases on

Table 6. Response of pulmonary metastases related to chemotherapy regimen

	Complete response	Partial or no response
Regimen 1	6	11
Regimen 2	7	3

the chest radiograph. Regimen 2, which included *cis*-diamminedichloroplatinum, was markedly more effective than regimen 1.

There was no significant correlation between the visible extent of pulmonary metastases as graded from the chest radiograph and any PFT. This is illustrated in Fig. 1, which shows VC values plotted against visible extent of pulmonary metastases (correlation matrix 0.24; non-significant). Similar results were obtained for the other PFTs.

The three patients who had received irradiation to a part of one lung before chemotherapy each received bleomycin with no signs of bleomycin pulmonary toxicity.

There were seven patients treated for metastatic testicular teratoma during the period considered who, for various reasons, received chemotherapy which significantly deviated from the regimens described. These patients have not been included in the general analysis. Three patients received a total dose of 180 mg bleomycin and four patients 270 mg bleomycin. In four patients the chemotherapy was modified because of general toxicity (nausea. vomiting and/or severe marrow toxicity) and in three patients because of progressive disease. None of these patients developed bleomycin toxicity.

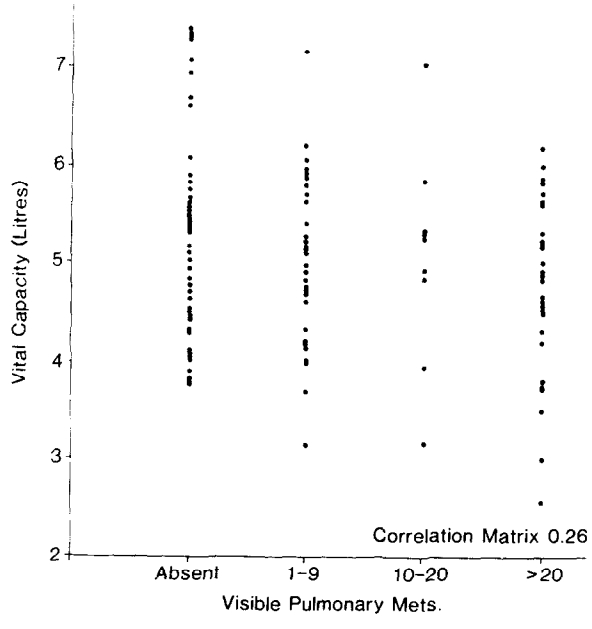

Fig. 1. Vital capacity related to visible extent of pulmonary metastases.

DISCUSSION

Several large series from throughout the world indicate that fatal bleomycin toxicity occurs in 1–2% of treated patients and non-fatal pulmonary fibrosis in an additional 2–3% [1, 8]. The greatest range in reported incidence occurs within groups termed 'questionable' or 'mild to moderate' toxicity and in those cases in which purely clinical criteria are used for diagnosis.

Samuels *et al.* [9] described two degrees of bleomycin-induced pulmonary toxicity which they termed 'minimal disease' and 'advanced disease'. 'Minimal disease' comprises exertional dyspnoea, dry cough, fine basal crepitations and either minimal or no changes in the chest radiograph. 'Advanced disease' comprises dyspnoea at rest, hypoxaemia ($pO_2 \leq$ 55 mm Hg) and prominent findings both on physical examination and on the chest radiograph. The changes of advanced disease are easily diagnosed, irreversible and may be fatal. The diagnosis of minimal disease can be very difficult, particularly in patients suffering respiratory symptoms from pulmonary metastases or those with coincidental lung disease.

Potential means of preventing advanced pulmonary toxicity include the following.

(a) *Avoidance of high total doses of bleomycin.* Adamson and Bowden [10], studying mice, found that histopathological lung changes of bleomycin toxicity are more severe with increasing total dose of bleomycin. A concensus of experience from a number of patient studies [1, 2, 4, 5, 8, 9, 11] suggests that there is a significant increase in pulmonary toxicity when total doses of bleomycin > 500 mg are used. Pulmonary toxicity also occurs in a relatively constant small proportion of cases receiving from 100 to 500 mg total doses of bleomycin. There is no evident dose–response relationship in this range. Einhorn and Donohue [5] reported data on 50 patients treated with vinblastine, bleomycin and *cis*-diamminedichloroplatinum in which the total dose limit of bleomycin was 360 mg (as in the currently reported series). They reported one case of fatal pulmonary toxicity.

It was thought, as a result of various studies, including that by Haas *et al.* [12], that intravenous bleomycin caused a higher overall incidence of pulmonary toxicity than the same dose given intramuscularly. More recent work has failed to confirm this. In the current series bleomycin was given intramuscularly in all cases.

From current evidence it seems likely that if the total dose of bleomycin does not exceed 360 mg, the number of cases of serious bleomycin pulmonary toxicity will be very small.

(b) *Detection of toxicity of serial PFTs.* Several studies are available which evaluate the relationship between bleomycin therapy and changes in PFTs [2, 4, 9, 12, 13]. Few studies have employed systematic serial determinations or clearly defined the timing of PFTs relative to total bleomycin dose or the cessation of bleomycin treatment. Within these constraints there have been reported changes in TLC, VC and DL_{CO}, but no consistent relationships with total bleomycin dose have been demonstrated. A fall in serially determined measurements of DL_{CO} with increasing bleomycin dose is the most commonly reported finding.

There were no cases of clinical pulmonary toxicity in our series despite the fall in DL_{CO} after 90 mg bleomycin, and the physiological significance of this finding at total bleomycin doses below 360 mg is negligible.

On current evidence routine serial PFTs do not appear to be necessary at total bleomycin dose levels < 360 mg, though they may be required in individual cases where there is some known exacerbating factor. We found no evidence of progressive pulmonary damage in patients cured of their disease and routine late PFTs appear unnecessary.

(c) *PFTs in patients with particular exacerbating factors.* Several studies [2, 8, 9, 14] indicate that prior or concomitant radiotherapy to the chest increases the incidence of significant bleomycin pulmonary toxicity, particularly when the irradiation encompasses the whole of both lungs. The three patients in the current series who had received irradiation to a part of one lung tolerated bleomycin without signs of toxicity. Nevertheless, it is advisable to monitor PFTs in patients who have received chest irradiation.

The incidence of pulmonary toxicity at a given dose level rises with age, particularly over the age of 70 yr. Thus, if older patients (> 50 yr) require chemotherapy, serial PFTs would seem a sensible precaution.

Grading of the extent of pulmonary metastases from the chest radiograph is relatively crude and it is hardly surprising that no statistically significant correlation with PFTs was found. In the generally young and previously fit patients included in this series, even quite extensive visible metastases on the chest radiograph seem to be associated with only minor disturbance in PFTs.

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