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Enhanced Pulmonary Toxicity in Smokers with Germ-cell Cancer Treated with *Cis*-Platinum, Vinblastine and Bleomycin: A Long-term Follow-up

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Abstract—*The long-term effects of bleomycin on pulmonary function were studied. Thirty-four patients with germ-cell cancer were followed for an average of 64 months (range 43–98 months). All had obtained complete remission during treatment and none had relapsed at the follow-up examination. Pulmonary function was tested by measurements of total lung capacity (TLC), vital capacity (VC), forced expiratory volume in one second (FEV_1) and single breath diffusion capacity for carbon monoxide (TL_{CO}). TLC and VC were significantly reduced by the treatment ($P < 0.05$), but normalized during the follow-up. TL_{CO} was initially reduced to a predicted median of 83%. In the smokers the initial TL_{CO} was at a predicted median of 79%, while in non-smokers a median of 88% was predicted. During the first 2 months of treatment, TL_{CO} increased both in smokers and non-smokers to predicted medians of 90% and 91%. Subsequently, however, a significant decrease to 72% was noted in the smokers, while the non-smokers had only an insignificant decrease to 84%. The decrease in TL_{CO} was irreversible but not progressive. We conclude that bleomycin treatment is associated with a long-term sustained reduction in TL_{CO}. The changes were most pronounced in the smokers.*

INTRODUCTION

BLEOMYCIN is used in most of the commonly applied treatment regimens for germ-cell cancer [1, 2]. The dose-limiting toxicity of bleomycin is interstitial pneumonia which was observed in 5–20% of the patients [3]. Fatal outcome has been reported in approximately 1% [4]. Since many of the patients are cured, a possible long-term toxicity of the chemotherapy may affect their quality of life for years. Studies dealing with long-term toxicity are few and usually do not cover more than 1–2 years follow-up [5–7]. The present study reports the results at 4–8 years follow-up in a group of germ-cell cancer patients with the aim of studying possible long-term pulmonary toxicity after treatment with bleomycin in combination with *cis*-platinum and vinblastine.

PATIENTS AND METHODS

Between March 1979 and December 1983 all patients referred to The Finsen Institute with metastatic non-seminomatous germ-cell cancer were treated with *cis*-platinum, vinblastine and bleomycin. The chemotherapy consisted of six courses of *cis*-platinum 20 mg/m^2 i.v., days 1–5, and vinblastine 6 mg/m^2 i.v., days 1 and 2 every 3 weeks. Bleomycin was given i.m. in a dosage of 15 mg/m^2 weekly for 10 weeks and thereafter as 5 mg/m^2 weekly for 8 weeks. Patients who obtained a complete response and had not relapsed were asked to participate in a follow-up examination evaluating pulmonary function. All participants gave fully informed consent. Before treatment, the lung function was tested by measurements of total lung capacity (TLC), vital capacity (VC), forced expiratory volume in one second (FEV_1) and single breath diffusion capacity for carbon monoxide (TL_{CO}) [8, 9]. TL_{CO} was corrected for deviations in hemoglobin concentration according to Dinakara *et al.* [10]. Bleomycin was discontinued if TL_{CO} decreased by more than 35%. The lung function tests were repeated before each cycle of chemotherapy, every 3 months after treatment for 2 years, and at the follow-up examination. The pulmonary function was compared with the laboratory's normal values based on a population sample of 125 non-smokers [11]. A chest roentgenogram was taken in association with each lung function testing.

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Table 1. Patient characteristics

	No. of patients
Total	34
Testicular cancer:	
Stage of disease	
II	19
IIIa	4
IIIb	9
Extragonadal	2
Age (median)	34 (range 19–54)
Smokers	20
Non-smokers	14
Cumulative dose of bleomycin	
median:	354 mg
range:	60–400 mg

For statistical analysis Student's *t*-test for paired samples was used to analyze changes in lung function during and after chemotherapy. Student's *t*-test for unpaired data was applied for the comparison of predicted and observed values. Patients were stratified retrospectively according to smoking habits. *P*-values <0.05 were considered significant.

RESULTS

Thirty-nine patients were eligible for the study. Two patients refused to participate, while three patients were excluded because pretreatment lung function tests had not been performed. The stage of disease and anthropometric data of the 34 evaluable patients are shown in Table 1. The median observation period was 64 months (range 43–98 months).

The results of the TLC, VC and FEV_1 measurements are given in Table 2. Both TLC and VC were significantly reduced during chemotherapy ($P < 0.05$), most importantly immediately after chemotherapy. After 15 months, the values had normalized and did not change later, FEV_1 was reduced before chemotherapy and remained stable at the reduced level during therapy. At follow-up, FEV_1 was still reduced to median 92% of the predicted value ($P < 0.05$), but had increased significantly compared with the pretreatment values. There were no differences in the TLC, VC and FEV_1 between smokers and non-smokers.

TL_{CO} was reduced before treatment (predicted median 83%, range 38–135%, $P < 0.05$) in both smokers (predicted median 79%, range 38–119%) and non-smokers (predicted median 88%, range 64–135%). In the patients who had had lymphangiography prior to treatment, pretreatment TL_{CO} was 83% predicted (range 64–107%) and did not differ significantly from the TL_{CO} median 81% predicted (range 38–135%) in the patients without pretherapeutic lymphangiography.

The results of the TL_{CO} measurements are shown in Table 3, and the time course of TL_{CO} (corrected for hemoglobin concentration) is depicted in Fig. 1. There was an *increase* in diffusion capacity during the first 2 months of chemotherapy to a predicted

Table 2. TLC, VC and FEV_1 expressed as a percentage of predicted value, median with upper and lower quartiles

	Pretreatment	2 months	5 months post-treatment	15 months	48+ months
TLC	100.5 (90–105)	100 (88–109)	91* (84–105)	99.5 (95–116)	99 (92–103)
VC	97.5 (88–107)	94.5 (81–102)	88.5* (75–98)	96 (90–108)	102 (93–109)
FEV_1	87.5 (74–93)	86.5 (79–93)	85 (76–95)	91 (84–96)	91 (85–102)

*Indicates $P < 0.05$.

Table 3. Hemoglobin (mmol/l), *TL_{CO} observed (percentage predicted) and TL_{CO} corrected for deviations in hemoglobin (percentage predicted) expressed as median (range)*

	Pretreatment	2 months	5 months post-treatment	15 months	48+ months
Hemoglobin mmol/l	9.2 (7.1–10.6)	7.6 (6.5–9.8)	7.7 (5.5–10.0)	9.1 (8.2–10.7)	9.0 (8.1–10.4)
TL_{CO} Observed	84 (33–128)	75 (28–139)	67 (42–94)	82 (42–109)	81 (43–125)
TL_{CO} Corrected	83 (38–135)	90 (39–158)	77 (39–136)	80 (50–106)	78 (44–124)

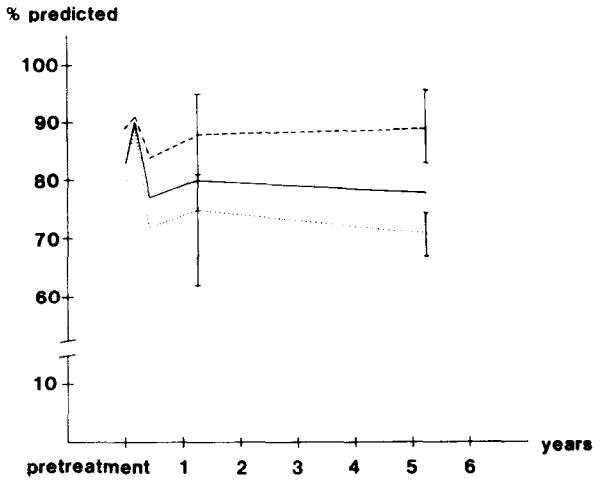

Fig. 1. Course of TL_{CO} over time in patients followed for 4–8 years. All 34 patients (median): ———. Smokers, 20 patients (median): ·····. Non-smokers, 14 patients (median): – – – – –. Bars indicate upper and lower quartiles.

median of 90% (range 39–118%) in smokers and 91% (range 53–158%) in non-smokers. This was followed by a significant decrease among the smokers reaching a minimum predicted median value of 72% (range 39–136%) immediately after the treatment. Among the non-smokers the initial increase was followed by an insignificant decrease.

DISCUSSION

The main histological changes in the lungs due to bleomycin therapy are endothelial changes, interstitial edema and fibrosis [12–14]. In patients followed for 1–2 years after treatment [5–7], reversibility of TL_{CO} seems to be related to the degree of bleomycin-induced toxicity observed during the treatment. In the present long-term follow-up, the decrease in TL_{CO} to 77% immediately after therapy remained unchanged during the observation period.

We found, in addition, that pretreatment TL_{CO} was significantly reduced. Similar observations have previously been made by others [6, 7, 15], and it was suggested that pretreatment lymphangiography might be the cause. In our group of patients TL_{CO} was not related to pretreatment lymphangiography. Alternatively, the pretreatment decrease in TL_{CO} may be associated with edema of the alveolar membrane caused by tumor products. This might explain the *increase* in TL_{CO} observed during the first 2 months of treatment when tumor regression was induced (Fig. 1), and before sufficient amounts of bleomycin had been accumulated to cause a measurable decrease in TL_{CO}. The subsequent reduction in TL_{CO} following further treatment with bleomycin was seen only in smokers.

In a recent paper by Lower *et al.* [16] bleomycin was shown to induce alveolar macrophage release of hydrogen peroxide in smokers. Local increases in PO_2 might conceivably enhance the toxicity induced by bleomycin. Enhanced toxicity has also been reported in patients treated with bleomycin, who were ventilated with high oxygen concentrations [17].

With regard to TLC, VC and FEV_1 no differences were found between smokers and non-smokers. The decrease in TLC and VC during treatment was fully reversible. The long-term effects of bleomycin therefore do not seem to influence the patients' ability to expand their lungs.

In conclusion, bleomycin treatment was associated with a sustained reduction in TL_{CO}. The changes were significantly most pronounced in smokers, but were not progressive.

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