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Short Communication

Enhanced Effects of Bleomycin on Pulmonary Function Disturbances in Patients with Decreased Renal Function Due to Cisplatin

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We examined whether cisplatin-induced nephrotoxicity augmented bleomycin-induced pulmonary toxicity in patients with testicular cancer treated with etoposide and cisplatin with (BEP) or without bleomycin (EP). Before and at 3-week intervals during chemotherapy, creatinine clearance and lung functions were measured. In patients receiving BEP, deterioration of renal function correlated with a decrease in transfer factor of the lungs for carbon monoxide (T_{LCO}) and vital capacity (VC), parameters known to reflect bleomycin-induced pulmonary effects. Other lung functions did not correlate with renal function. In the EP group, no relationships were observed at all. These observations suggest enhanced pulmonary effects of bleomycin when combined with cisplatin. Therefore, attention should be paid to the potential development of bleomycin-induced pulmonary toxicity in patients treated with BEP.

Key words: bleomycin, cisplatin, testicular cancer, lung function, renal function
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INTRODUCTION

MANY REGIMENS for disseminated testicular cancer combine bleomycin with cisplatin. The most feared disadvantage of bleomycin is bleomycin-induced pneumonitis (BIP) [1], while cisplatin is known for its nephrotoxicity [2].

Bleomycin is mainly excreted by the kidneys [3], and several reports have shown a relationship between deterioration of renal function and development of bleomycin-induced pulmonary toxicity [4–9]. Recently, we showed that the frequently used transfer factor of the lungs for carbon monoxide (T_{LCO}) is not suitable to establish pulmonary toxicity from bleomycin in the combination bleomycin, etoposide and cisplatin (BEP) [10]. However, the capillary blood volume of the lungs (V_C), one of the components of T_{LCO}, as well as the vital capacity (VC) do measure pulmonary changes specifically. Moreover, we showed that when BIP occurs, lung function parameters completely normalise in time [11].

In this study, we explored whether the decrease in renal function caused by cisplatin is correlated with a decrease in pulmonary function due to bleomycin. We performed creatinine clearance and lung functions in patients with testicular cancer treated with BEP or with etoposide and cisplatin (EP) in a randomised phase III trial of the EORTC GU Group [12].

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PATIENTS AND METHODS

54 patients with low volume metastases [10] of a non-seminomatous testicular tumour were randomised. 27 patients were treated with four cycles of BEP, consisting of cisplatin 20 mg/m^2 i.v. on days 1–5, every 3 weeks for 12 weeks, etoposide 120 mg/m^2 i.v. on days 1, 3, 5, every 3 weeks for 12 weeks and bleomycin 30 mg dissolved in 100 ml 0.9% NaCl intravenously infused in 15 min, on day 2 and thereafter weekly for 12 weeks. 27 patients received four cycles of EP, cisplatin and etoposide only.

Before and at 3-week intervals during treatment, creatinine clearance using the Cockroft-formula [13], and lung function were determined.

Slow inspiratory vital capacity (VC) was performed with a standard spirometer. T_{LCO} was determined using a modified single breath technique as described previously [10]. The two components of T_{LCO}, the alveolo-capillary membrane (D_M) and the capillary blood volume of the lungs (V_C), were calculated from measuring T_{LCO} at two oxygen concentrations (18.4 and 88.0%) [10]. The alveolar volume (V_A) was calculated from the inspiratory and expiratory helium concen-

trations during determination of T_{LCO}. The transfer factor of the lungs for carbon monoxide per unit alveolar volume (K_{CO}) was obtained by dividing T_{LCO} by V_A. Lung function values were expressed as the percentage predicted value [10].

BIP was defined as previously described [1].

For analysing correlations between creatinine clearance and lung functions, data were pooled and examined by Pearson's correlation (two-tailed).

Analysis of variance (ANOVA) in a repeated measurement design was used to compare changes in functions to pretreatment values. Differences between both groups were analysed by two-tailed unpaired Student *t*-tests. *P* values below 0.05 were considered as significant.

RESULTS

Between both groups, there were no differences in factors that may influence renal or pulmonary functions such as age and smoking habits. Patients' characteristics and pretreatment values of renal and lung functions are shown in Table 1.

After chemotherapy, creatinine clearance was decreased compared to pretreatment values in both groups (BEP, $P = 0.002$; EP, $P = 0.015$). Values after the fourth cycle were equal in both groups, in the BEP group 120 ml/min (S.D. = 24 ml/min) and 120 ml/min (S.D. = 21 ml/min) in the EP group. The decline expressed as percentage of pretreatment value also did not differ significantly, 18% and 12% in the BEP and EP groups, respectively.

3 patients in the BEP group developed BIP during the fourth cycle. Their creatinine clearance was not notably different from other patients receiving BEP after the third cycle.

Changes of lung function during treatment have been described previously [10]. Briefly, T_{LCO}, D_M and K_{CO} decreased significantly during treatment in both groups, while V_C and VC declined only in the BEP group and remained stable in the EP group.

In the BEP group, a significant association was observed between T_{LCO} and creatinine clearance ($r = 0.29$; $P = 0.001$). This relationship was not seen in the EP group ($r = -0.0661$; $P = 0.462$). The two components of T_{LCO}, D_M and V_C, were not related to renal function neither in the BEP group ($r = 0.1726$; $P = 0.059$ and $r = 0.1326$; $P = 0.149$) nor in the EP group ($r = -0.1201$; $P = 0.189$ and $r = -0.1526$; $P = 0.095$), respectively.

VC and creatinine clearance were significantly related in the BEP group but not in the EP group ($r = 0.2011$; $P = 0.025$ and $r = -0.1427$; $P = 0.111$, respectively).

Between renal function and K_{CO} no correlation was found in both groups (BEP: $r = 0.1133$; $P = 0.212$ and EP: $r = -0.0007$; $P = 0.994$).

DISCUSSION

The most feared side-effect of bleomycin is pulmonary toxicity [1]. Renal dysfunction augments bleomycin-induced toxicity because bleomycin is mainly eliminated by the kidneys [3]. Consequently, amelioration of renal function prolongs this excretion [14]. Combining bleomycin with drugs which adversely affect renal function has enhanced bleomycin-induced pulmonary toxicity [4, 5, 8] expressed by a decrease in T_{LCO} [4, 8]. We found that a decline in renal function is significantly related to a decrease in T_{LCO} in patients receiving bleomycin with etoposide and cisplatin, which suggests an increased toxic effect of bleomycin on the lungs when renal function is progressively impaired. In patients treated with EP, no such relation was observed.

However, we showed previously that the widely used T_{LCO} is not a proper tool for detecting pulmonary damage caused by bleomycin, but the components of T_{LCO}, the capillary blood volume of the lungs (V_C) and the vital capacity (VC), were suitable [10]. The significant positive correlation between VC and creatinine clearance, found in the BEP group, suggests that there is indeed an augmented toxic effect of bleomycin on the pulmonary function when renal function is impaired.

The observation that V_C, also specific for bleomycin-induced pulmonary damage, is not related to renal function in patients receiving BEP may indicate that VC is a more sensitive parameter.

Previously, we have shown that patients treated with BEP as well as with EP had a similar decrease of the diffusing capacity of the alveolo-capillary membrane (D_M) [10]. It can be assumed that bleomycin has only a minor, if any, direct impact on D_M and that alterations of D_M are mainly caused by etoposide and/or cisplatin. As etoposide is not known for inducing a decline in renal function, the observation that D_M and renal function are not related may indicate that either alterations in D_M are caused by etoposide or that cisplatin induces effects in lung and kidneys by different mechanisms.

In conclusion, this study shows that changes of T_{LCO} and

Table 1. Patients' characteristics

	Etoposide and cisplatin with bleomycin (BEP)	Etoposide and cisplatin without bleomycin (EP)	
No. of patients	27	27	
Mean age in years (range)	31 (21–44)	31 (17–51)	
Smoking history (no. of patients)	9	11	
Mean creatinine clearance in ml/min (S.D.)	145 (26)	136 (26)	
Mean pretreatment value in % predicted value (S.D.)			
T_{LCO}	96 (13)	92 (15)	
V_C	87 (16)	78 (15)	$P = 0.038$
D_M	97 (19)	99 (22)	
VC	90 (17)	94 (12)	
K_{CO}	97 (19)	89 (11)	$P = 0.035$

T_{LCO}, transfer factor of the lungs for carbon monoxide; V_C, capillary blood volume of the lungs; D_M, diffusing capacity of the alveolo-capillary membrane; VC, vital capacity; K_{CO}, transfer factor of the lungs for carbon monoxide per unit alveolar volume.

VC, being parameters for bleomycin-induced pulmonary changes, are positively correlated with changes in creatinine clearance. This suggests enhanced effects on the lungs by bleomycin when combined with drugs which can induce renal dysfunction, such as cisplatin.

Therefore, in patients treated with BEP for disseminated testicular cancer who develop a decrease in renal function, special attention should be paid to the potential development of bleomycin-induced pulmonary toxicity.

1. Comis RL. Bleomycin pulmonary toxicity: current status and future directions. *Semin Oncol* 1992, **19** (Suppl. 5), 64–70.
2. Dentino M, Luft FC, Yum NM, Williams SD, Einhorn LH. Long term effect of cis-diamminechloroplatinum (CDDP) on renal function and structure in man. *Cancer* 1978, **41**, 1274–1281.
3. Okew MM, Crooke ST, Elson MK, Strong JE, Shafer RB. Pharmacokinetics of bleomycin after administration in man. *Cancer Treat Rep* 1981, **65**, 485–489.
4. Dalgleish AG, Woods RL, Levi JA. Bleomycin pulmonary toxicity: its relationship to renal function. *Med Ped Oncol* 1984, **12**, 313–317.
5. Petrilli ES, Castaldo TW, Matutat RJ, Ballon SC, Gutierrez ML. Bleomycin pharmacology in relation to adverse effects and renal function in cervical cancer patients. *Gynecol Oncol* 1982, **14**, 350–354.
6. McLeod BF, Lawrence HJ, Smith DW, Vogt PJ, Gandara DR. Fatal bleomycin toxicity from a low cumulative dose in a patient with renal insufficiency. *Cancer* 1987, **60**, 2617–2620.
7. Perry DJ, Weiss RB, Taylor HG. Enhanced bleomycin toxicity during acute renal failure. *Cancer Treat Rep* 1982, **6**, 592–593.
8. Van Barneveld PWC, Sleijfer DT, Van der Mark TW, *et al.* Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular cancer. *Oncology* 1984, **41**, 4–7.
9. Bennet WM, Pastore L, Houghton IC. Fatal pulmonary bleomycin toxicity in cisplatin induced acute renal failure. *Cancer Treat Rep* 1980, **64**, 921–924.
10. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH. Decrease in pulmonary function during bleomycin containing combination chemotherapy for testicular cancer: not only a bleomycin effect. *Br J Cancer* 1995, **71**, 120–123.
11. Van Barneveld PWC, Sleijfer DT, van der Mark TW, *et al.* The natural course of bleomycin induced pneumonitis (BIP)—a follow up study in eight patients. *Am Rev Respir Dis* 1987, **135**, 48–51.
12. Stoter G, Kaye S, Jones W, *et al.* Cisplatin and VP-16 +/– bleomycin (BEP vs EP) in good risk patients with disseminated nonseminomatous testicular cancer: a randomized EORTC GU Group study. *Proc Am Soc Clin Oncol* 1987, **6**, 110.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976, **16**, 31–41.
14. Crooke ST, Comis RL, Einhorn LH, Strong JE, Broughton A, Prestayko AW. Effects of variations in renal function on the clinical pharmacology of bleomycin administered as an IV bolus. *Cancer Treat Rep* 1987, **61**, 1631–1636.