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Short communication

Bleomycin lung: the effect of different chemotherapeutic regimens

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Summary. A review of hard-copy computed tomography (CT) images of patients who had undergone chemotherapy for testicular teratoma revealed that the incidence of lung toxicity appeared to be lower in those who had received bleomycin by slow infusion [EBCi (3) regimen, etoposide/bleomycin/cisplatin] rather than by intravenous bolus [PVB regimen, cisplatin/vinblastine/bleomycin; BEP (5) regimen, bleomcycin/etoposide/cisplatin]. This difference reached statistical significance only for PVB vs EBCi (3) ($t = 2.63$, $P < 0.01$). Nevertheless, in view of continuing reports of mortality resulting from bleomycin-induced pulmonary fibrosis in patients receiving the drug by i. v. bolus, further exploration of these results is clearly justified.

Introduction

Over the last decade, the overall results of chemotherapeutic treatment for metastatic malignant teratoma have improved from a cure rate of 60% [4, 11] to the current figure of approximately 90%, due largely to increasing experience and to an awareness of the need for early treatment [7a]. However, such treatment has always carried a small risk of lethal toxicity, and bleomycin-induced lung toxicity and cisplatin-related nephrotoxicity have become the most serious complications.

Bleomycin, which is widely used in combination chemotherapy regimens, particularly for the treatment of testicular cancer, is well known for producing pulmonary toxicity [5, 6]. It has been suggested that the major determinant of Bleomycin lung toxicity is the cumulative dose [3], but other investigators [10] have been unable to substantiate this. The changes in pulmonary toxicity are more sensitively shown on computed tomography (CT) than on plain film radiography [1], and quantitative methods of assessing the degree of toxicity have been described by Rimmer et al. [10] and Bellamy et al. [2]. The same authors have also found some reversibility for these observed pulmonary changes.

Following suggestions that pulmonary toxicity was not seen in patients receiving bleomycin by continuous infusion (Newlands, personal communication; Samuels, personal communication) as opposed to standard i. v. pulsed therapy, workers first at the London Hospital and later at Addenbrooke's Hospital used a modification of the standard 5-day pulsed bleomycin, etopside and cisplatin (BEP) combination. In this new regimen (EBCi), a smaller dose of bleomycin is given as an 8-h infusion on the first 3 days of treatment rather than being injected as an i. v. bolus on a number of different days. Initial results [8] suggested that this 3-day modification of the standard 5-day BEP regimen was at least as effective as earlier combinations, and possibly less toxic.

This report describes the degree of pulmonary toxicity caused by the two bleomycin, etopside and cisplatin chemotherapy regimens as well as by the classic PVB regimen of cisplatin, vinblastine and bleomycin as determined on serial CT examinations.

Patients and methods

The post-treatment CT data on 57 consecutive patients who had been treated with one of the three regimens deseribed above (Table 1) were evaluated in the present study. In all, 13 patients had been treated with PVB, receiving bolus bleomycin (30 mg) on days 2, 9 and 16 [4]; 26 had undergone therapy with BEP [5-day cisplatin with i. v. bolus injection of bleomycin (30 mg) on days 2, 9 and 16 [9]]; and 18 had been treated with the newly described regimen (EBCi) whereby bleomycin (15 mg) is given on 3 days, but by infusion rather than i. v. bolus [8].

Quantitative assessment was achieved by the method outlined by Rimmer et al. [10], whereby each CT examination was studied and the numbers of involved sections were expressed as a proportion of the total. When there was more than one post-treatment CT study, that showing the greatest changes typical of bleomycin toxicity was chosen for the analysis. Student's *t*-tests were used for statistical analysis of differences in the actual percentage of CT sections involved between the three groups of patients who had been treated with the different regimens.

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Table 1. Chemotherapy regimens evaluated in the present study

	Day						
	1	2	3	4	5	9	16
PVB: (q21d)							
Cisplatin (mg/m^2)	20	20	20	20	20		
Vinblastine (mg/kg)	1.5	1.5					
Bleomycin (mg)	30					30	30
BEP (q21d):							
Cisplatin (mg/m^2)	20	20	20	20	20		
Etoposide (mg/m^2)	120	120	120	120	120		
Bleomycin (mg)	30					30	30
EBCi (3):							
Cisplatin (mg/m^2)	40	40	40				
Etoposide (mg/m^2)	120	120	120				
Bleomycin (mg)	30						

Results

The proportion of involved sections was calculated for each patient, and the results are displayed in Fig. 1. Changes in pulmonary toxicity were noted to occur predominantly in a peripheral and posterior sub-pleural location, and nearly all subjects showed some improvement in their pulmonary changes on sequential scans.

Pulmonary involvement was noted in 10 of 13 (78%) patients who had been treated with PVB, in 18 of 26 (69%) who had received BEP (5) and in 8 of 18 (44%) who had been given EBCi (3). The application of Student's t-test to the actual percentage of CT cuts involved revealed a statistically significant reduction in the pulmonary involvement produced by EBCi (3) as compared with PVB ($t = 2.63$, $P < 0.01$). However, no significant difference was found in the involvement produced by BEP (5) vs EBCi (3) ($t = 1.56$, $P > 0.1$) or in that caused by PVB vs BEP (5) ($t = 0.91$, $P > 0.5$).

None of the patients who had been treated on the EBCi (3) infusion schedule developed severe changes (grade 3) involving greater than 75% of their sections. Only one patient died of progressive respiratory failure following treatment with the BEP (5) i.v. bolus regimen.

Discussion

The distribution of bleomycin-induced changes reported in this study are in accordance with those previously reported by Bellamy et al. [1] and Rimmer et al. [10], and our results suggest that their incidence was lower in patients who had received the EBCi (3) regimen.

There is some evidence that it may be safe not to use bleomycin in patients with germ-cell tumours of small volume [2a, 10a]. However, recent observatins by Loehrer et al. [7], who reported treatment failure in 26 of 83 (31%) subjects receiving EP as compared with 13 of 83 (16%) patients receiving BEP, suggest that this is issue has not been satisfactorily resolved. However, the hazard of associated pulmonary toxicity remains very real, accounting for approximately half of the overall 5.1% treatment-related mortality in patients with advanced disease as recently reported by Einhorn's group [12].

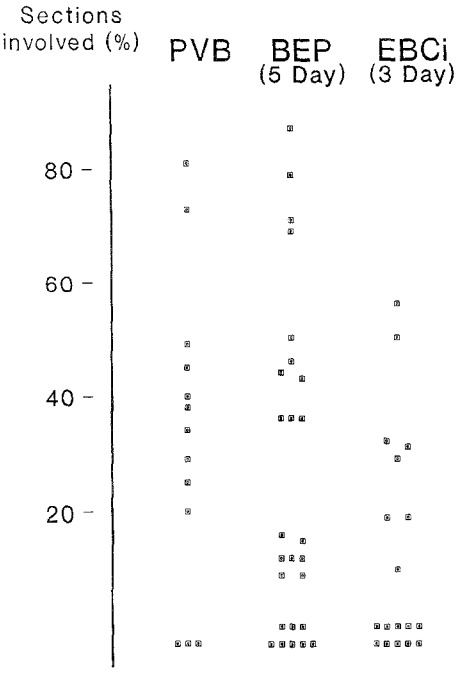

Fig. 1. Incidence of bleomycin-induced fibrotic changes on CT scans taken after the administration of chemotherapy to patients with metastatic testicular tumours. Each point equals the proportion of CT lung images showing changes in an individual patient

More than 10 years have elapsed since the findings of both Newlands and Samuels (unpublished observations) that lung toxicity did not occur in patients receiving bleomycin by infusion rather than by i.v. bolus. It was these observations that encouraged us to pursue the studies reported in this paper. Due to differences in dosage as well as in the duration of infusion in the protocols evaluated, no definitive conclusion can be drawn from the results presented. However, in view of the life-threatening potential of these complications of bleomycin therapy and of the observation that both the BEP vs BEC and the BOP/VIP vs BEP protocols launched by the Medical Research Council permit the use of the 30-mg i.v. bolus regimen, we felt justified in reporting these results so as to stimulate further examination of the problem.

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