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Short communication

Pulmonary toxicity in patients with non-Hodgkin's lymphoma treated with bleomycin-containing combination chemotherapy

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Abstract. Subclinical and clinical bleomycin-induced pulmonary toxicity (BIP) were investigated retrospectively in 109 patients with non-Hodgkin's lymphoma treated by combination chemotherapy containing bleomycin. A decrease in carbon monoxide diffusing capacity (DLCO) was found in 12.8% of patients. The cumulative risk of abnormal DLCO increased with the increasing total cumulative dose of bleomycin. No significant difference in the rate of BIP was observed between patients receiving bleomycin/Adriamycin/cyclophosphamide/vincristine/prednisone (BACOP; bleomycin given at 10 mg/m^2 for 4 weeks) and bleomycin/Adriamycin/cyclophosphamide/vincristine/dexamethasone/methotrexate/folinic acid (m-BACOD; bleomycin given at 4 mg/m^2 for 3 weeks, methotrexate given at 200 mg/m^2. Monitoring for subclinical BIP should be considered in patients with non-Hodgkin's lymphoma even if only a low dose of bleomycin was given in the presence of other chemotherapeutic agents.

Introduction

Bleomycin is active against lymphoma, especially when used in combination with other chemotherapeutic agents [6, 9]. Although bleomycin is not marrow toxic, it induces interstitial pneumonitis, which is potentially lethal [2, 7, 9]. Subclinical bleomycin-induced pulmonary toxicity (BIP) can be picked up by pulmonary function testing (PFT) [6, 10].

It is not clear whether serial PFT can predict the development of BIP and be adequate to avoid progression. We undertook a retrospective study of patients receiving bleomycin-containing combination chemotherapy for the treatment of non-Hodgkin's lymphoma to detect BIP by means of serial PFT.

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Patients and methods

During the period 1984–1989, 109 patients with intermediate- to high-grade non-Hodgkin's lymphoma were recruited in this retrospective study. These patients had normal pretreatment PFT and underwent serial PFT once every month during bleomycin combination chemotherapy. In all, 58 patients received BACOP (5 mg/m^2 bleomycin given by i.v. infusion on days 15 and 22; 25 mg/m^2 Adriamycin given by i.v. infusion on days 1 and 8; 650 mg/m^2 cyclophosphamide given by i.v. infusion on days 1 and 8; 1.4 mg/m^2 vincristine given by i.v. infusion on day 1; and 60 mg/m^2 prednisone given orally on days 15–28; courses were repeated every 4 weeks) and 51 patients received m-BACOD (4 mg/m^2 bleomycin given by i.v. infusion on day 1; 45 mg/m^2 Adriamycin given by i.v. infusion on day 1; 600 mg/m^2 cyclophosphamide given by i.v. infusion on day 1; 1 mg/m^2 vincristine given by i.v. infusion on day 1; 6 mg/m^2 dexamethasone given orally on days 1–5; 200 mg/m^2 methotrexate given by i.v. infusion on days 8 and 15; and 15 mg folinic aicd $\times 6$ given orally; courses were repeated every 3 weeks).

Both carbon monoxide diffusing capacity (DLCO) and forced expiratory volume (FVC) were assessed with the Gould 5000 IV Computerised Pulmonary Function System. FVC was measured with the rolling-seal spirometer, and DLCO was measured by the single-breath technique. Data reported by Da Costa [5] and Crapo and Morris [4] were used as references for normal values. Subclinical BIP was diagnosed when PFT showed a decrease of more than 35% in DLCO or FVC in relation to the baseline value [6]. DLCO measurements were corrected for haemoglobin (Hb) concentration by the formula:

$$\text{DLCO (corrected)} = \text{DLCO (observed)} \times \frac{10.2 + \text{Hb}}{1.7 \times \text{Hb}}$$

with Hb being expressed in grams per deciliter [1]. Treatment with bleomycin was withheld if the patient developed subclinical BIP. Clinical BIP was diagnosed on the basis of the following features: persistent dyspnoea, non-productive cough, fine rales on auscultation and typical bi-basilar reticular or fine nodular infiltrates on chest radiography without other pulmonary cause [2, 7].

Risk factors that predispose patients to pulmonary toxicity, such as age, smoking habits, impaired renal function, lung or pleural metastasis, radiotherapy to the lung and the dose of bleomycin given, were assessed.

Statistical analysis was performed using the chi-square test. The cumulative hazard of increasing total bleomycin dose with abnormal PFT

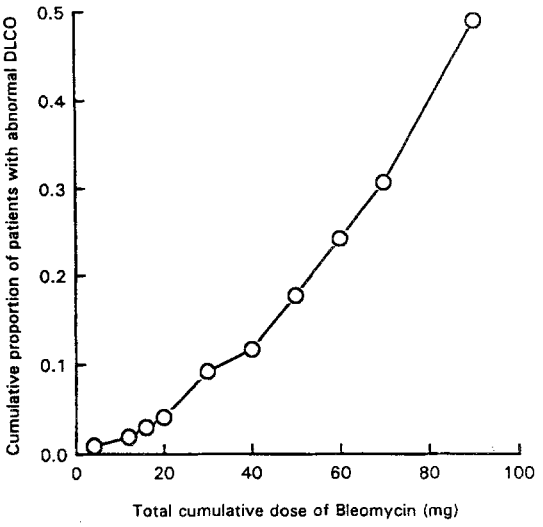

Fig. 1. Cumulative risk of abnormal DLCO with cumulative total dose of bleomycin

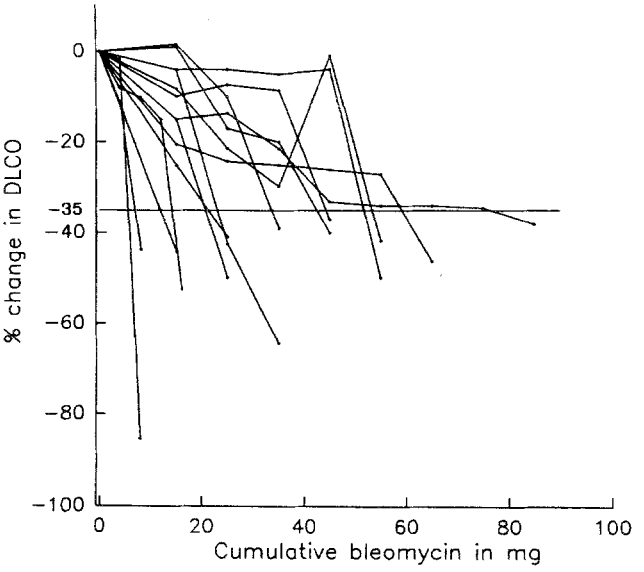

Fig. 2. Serial percentage of change in DLCO with cumulative bleomycin dose (in mg) in 14 patients with impaired DLCO during treatment

was plotted using the BMDP statistical software programme (BMDP Statistical Software Inc., 1990 version).

Results

The age of the 109 patients ranged from 15 to 74 years (mean $\pm$SD, 46.1 $\pm$ 15.5 years). There was no significant association of abnormal PFT with an age of more than 60 years. All patients had normal renal function. Only 30.3% of the patients were smokers. There was no significant association of abnormal PFT with smoking. None of the 7 patients with lung or pleural metastasis had impaired PFT. In all, 4 patients received concomitant radiotherapy to the mediastinum or the lung; 2 of them (50%) had impaired PFT and 1 of them developed clinical BIP.

The total number of courses of BACOP or m-BACOD given ranged from 1 to 9 (mean, 3.9); 55% of the patients received 6 or more courses. The total dose of bleomycin delivered to the patients ranged from 4 to 90 mg (mean $\pm$SD, 38 $\pm$ 23.7 mg). A graph of the cumulative risk of abnormal PFT with increasing total dose of bleomycin is shown in Fig. 1. The cumulative risk of abnormal PFT after a total dose of 90 mg bleomycin was 0.49.

In all, 14 of the 109 patients (12.8%) developed abnormal PFT while on treatment. All of them had impaired DLCO and normal FVC. The serial changes in DLCO with reference to pre-treatment measurements showed a progressive decrease with increasing cumulative bleomycin dose (Fig. 2). Of these 14 patients, 11 received BACOP and 3 received m-BACOD. There was no significant difference in the proportion of patients with abnormal PFT or in the cumulative risk of impaired PFT between the two groups of patients receiving BACOP or m-BACOD.

Only 1 patient (0.9%) developed clinical BIP. DLCO fell from 133 to 25 ml min^{-1} $mmHg^{-1}$ (that is, only 19% of the pre-treatment value) after 1 course of m-BACOD. He was also receiving radiotherapy to the mediastinum. After the omission of bleomycin from subsequent courses of chemotherapy, his PFT returned to normal values within 4 months.

Discussion

BIP is a potentially lethal complication. Van Barneveld et al. [10] reported a significant fall in DLCO only after a cumulative dose of 360 mg in the treatment of testicular carcinoma. However, a higher incidence of BIP was found in patients with non-Hodgkin's lymphoma treated with a lower cumulative dose of bleomycin in combination chemotherapy [2, 8]. In the present study, an increasing risk of abnormal DLCO was found with increasing cumulative total dose of bleomycin, even at doses below 90 mg. For patients with subclinical BIP, the fall in DLCO was progressive with increasing dose, and the varying rate could indicate individual susceptibility.

Shapiro et al. [8] have suggested that methotrexate may play an important role in the pathogenesis of pulmonary toxicity in a study comparing pulmonary toxicity among patients receiving m-BACOD, m-ACOD (m-BACOD minus bleomycin) and CHOP. No pulmonary toxicity was observed in the CHOP group. However, the present study failed to support this hypothesis, since no significant difference in the occurrence of BIP was observed between patients receiving m-BACOD (containing methotrexate) and those receiving BACOP (without methotrexate). A further control study in a larger number of patients may help to define the role of methotrexate.

We conclude that DLCO is a better parameter than FVC for the detection of subclinical BIP. The 12.8% incidence of subclinical BIP observed in this study was found among patients with non-Hodgkin's lymphoma treated by combination chemotherapy containing bleomycin. The risk of abnormal DLCO increased with increasing cumulative total dose of bleomycin.

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