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Changes in pulmonary function during and after bleomycin treatment in patients with testicular carcinoma

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Summary. *Pulmonary function tests, including spirometry, transfer factor of the lungs for carbon monoxide (TlCO), and the two components of TlCO, the diffusing capacity of the alveolocapillary membrane (Dm) and pulmonary capillary blood volume (Vc), were carried out in a group of patients with testicular carcinoma during and after treatment with the Einhorn regimen. The lung function parameters of patients who developed bleomycin-induced pneumonitis were compared with those recorded in a group of patients who did not develop this syndrome.*

We suggest that bleomycin-induced damage to the pulmonary capillary vasculature can be monitored by measuring Vc and that ensuing fibrosis can be measured by recording Dm. The decrease in Dm is probably compensated for by an increase in Vc, leading to a smaller change in TlCO.

Introduction

Bleomycin, an antitumor antibiotic, has been used as a single agent or in combination chemotherapy schedules in the treatment of various malignancies [2]. The dose-limiting factor, however, is its pulmonary toxicity [2, 5]. Following observation of the effects of bleomycin on lung function, it has been reported that the single-breath carbon monoxide transfer factor (TlCO) is a sensitive indicator of pulmonary toxicity [6, 11], but that the most striking phenomenon is a decrease in capillary blood volume [12].

In this prospective study we evaluated, in a well-defined group of patients, the influence of bleomycin on different lung function parameters during and after therapy. Changes in these parameters in a subgroup of patients developing signs and symptoms of bleomycin-induced pneumonitis (BIP) were compared with those in the other patients.

Materials and methods

We made a prospective study of 43 patients being treated for disseminated testicular carcinoma at the Universtiy Hospital of Groningen, The Netherlands. All patients were treated with four cycles of combination chemotherapy with *cis*-diammine-dichloroplatinum (cisDDP), vinblastine, and bleomycin, as detailed by Einhorn [8]. After prehydration, *cis*-DDP 20 mg/m^2 was infused on 5 consecutive days, followed by adequate posthydration. On day 1 and day 2 of each cycle, vinblastine 0.15–0.20 mg/kg daily was given. On day 2, and at weekly intervals for 12 weeks, bleomycin 30 mg was given in a 15-min infusion. Before the start of chemotherapy and at 3-week intervals during remission-induction therapy lung function tests were done. After the therapy the same lung function tests were performed at 6-week intervals. Slow vital capacity (VC) and forced expiration volume in 1 s (FEV_1) were measured with a standard water-sealed spirometer. Pretreatment values of VC and FEV_1 were expressed as liters at body temperature and pressure 9 saturated (BTPS). The TlCO was measured with the single-breath technique of Krogh [10] as modified by Ogilvie [13] and Cotes [7]. The TlCO values, breathing air, were corrected for abnormal hemoglobin concentrations according to Hilpert [9] to obtain TlCO values under standard conditions. The TlCO was expressed in millimoles per kilopascal per minute.

The two components of TlCO, the diffusing capacity of the alveolocapillary membrane (*Dm*) and the pulmonary capillary blood volume (*Vc*), were determined from measurements of TlCO at high (88%) and low (18.4%) inspiratory oxygen concentration. The calculation follows the equation originally devised by Roughton and Forster [14]:

$$1/\mathrm{TlCO} = 1/Dm + 1/\vartheta[Hb]Vc,$$

where ϑ is the reaction rate of carbon monoxide with oxyhemoglobin at the average normal hemoglobin concentration of 14.6 g/100 ml; and $[Hb]$ is the hemoglobin concentration as a fraction of normal. Since the hemoglobin concentration appears explicitly in this equation, no correction for *Hb* is needed. A detailed description of the determination of *Dm* and *Vc* is given by Cotes [7]. These measurements were performed in duplicate. *Vc* was expressed in milliliters and Dm in millimoles per kilopascal per minute. Alveolar volume (*VA*) was calculated from the inspiratory and expiratory helium concentrations measured during the single-breath maneuver necessary for the determination of TlCO. The initial value of each lung function test for each patient was set at 100%. The values measured during and after chemotherapy were expressed as percentage changes of the initial value. Changes in lung function parameters were related to the total cumulative dose of bleomycin and to the cumulative dose of bleomycin per body surface area.

Bleomycin-induced pneumonitis (BIP) was defined as a clinical syndrome in which the patients complained of cough

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and/or exertional dyspnea. Physical findings consisted of fine bilateral basal rales, coarse rales over in the lower one-third of the lung fields, and/or pleura rub, feber, and/or cyanosis. Radiographic findings included fine (bilateral basal) infiltrates or progressive lower lobe involvement or consolidation [5]. The patients who did not develop signs or symptoms of BIP were classified as group I, the patients with BIP as group II.

Statistical analyses were performed with reference to Student's *t*-test.

Results

During the remission-induction chemotherapy for disseminated testicular carcinoma we studied 43 previously untreated patients (mean age 29.6 years, range 17–48 years), 19 of whom had pulmonary metastases while none had pre-existing pulmonary disease. The group included 25 smokers. Of the initial number of 43 patients, eight developed BIP. The remaining 35 patients included 18 who were eligible for follow-up investigations. The other 17 patients were not eligible because of insufficient data, tumor relapse, or thoracic surgery for removal of residual tumor. The groups of patients (I and II) had the same characteristics with regard to age, the presence of pulmonary metastases, smoking habits, and tumor markers.

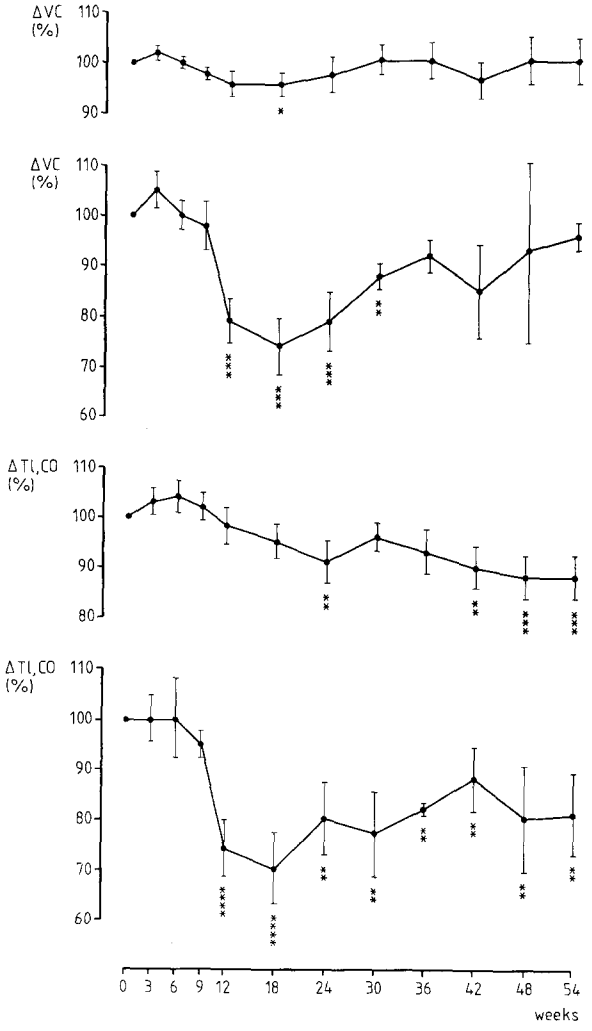

Fig. 1. The relation between time in weeks and the relative change in *VC* in group I (*above*) and group II (*below*) and TlCO in group I (*above*) and group II (*below*). Pretreatment values are 100%. $^{*}P < 0.05$; $^{**}P < 0.025$; $^{***}P < 0.005$; $^{****}P < 0.0025$

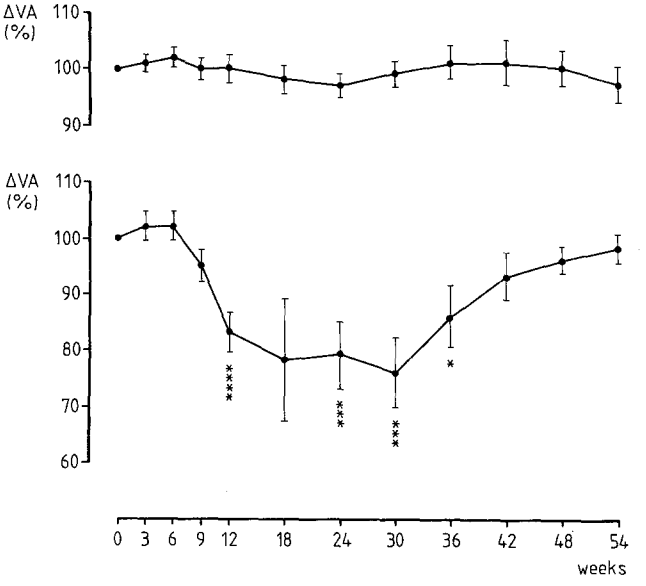

Fig. 2. The relation between time in weeks and the relative change in *VA* in group I (*above*) and group II (*below*). Pretreatment values are 100%. $^{*}P < 0.05$; $^{***}P < 0.005$; $^{****}P < 0.0025$

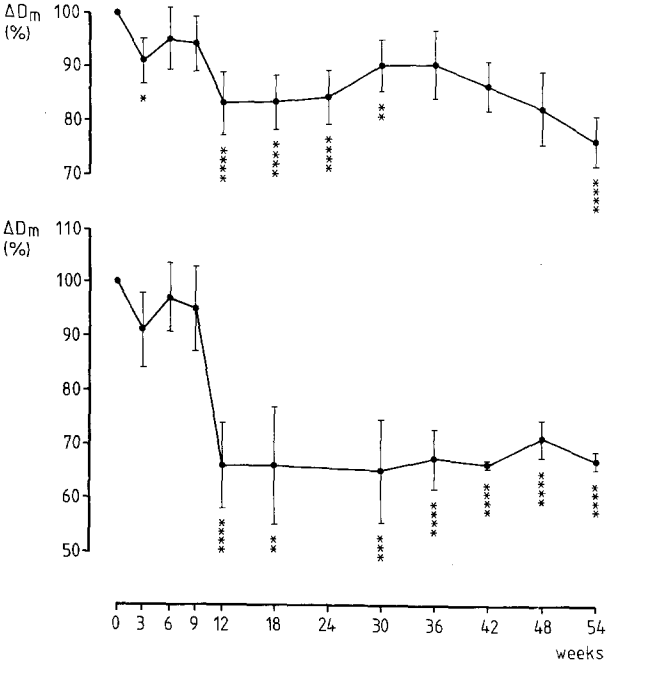

Fig. 3. The relation between time in weeks and the relative change in *Dm* in group I (*above*) and group II (*below*). Pretreatment values are 100%. $^{**}P < 0.025$; $^{***}P < 0.005$; $^{****}P < 0.0025$

In group I, without BIP, the VC showed a tendency to decrease, only reaching significance at 18 weeks ($P < 0.05$). In group II, the BIP group, the VC was significantly decreased at 12 weeks ($P < 0.005$), while at the end of the follow-up period initial values were reached again (Fig. 1).

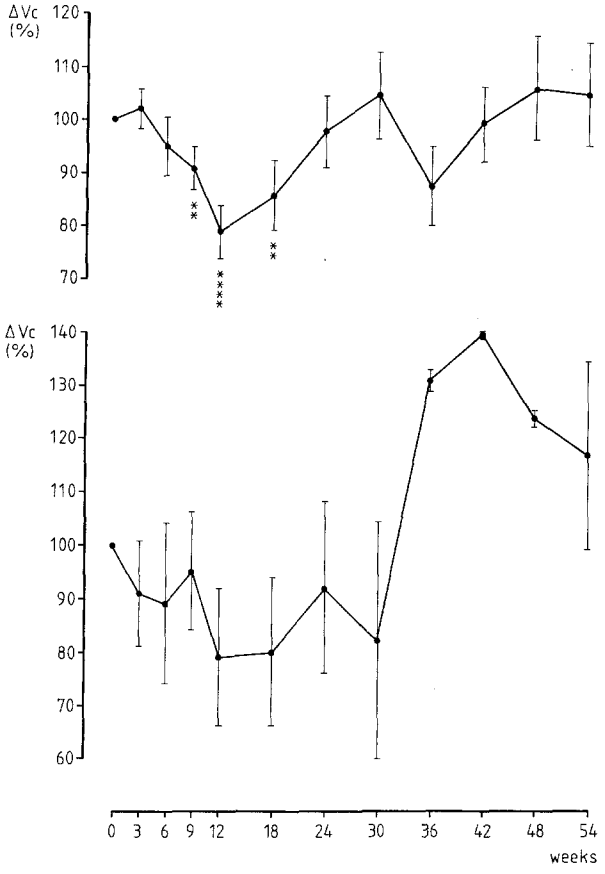

Fig. 4. The relation between time in weeks and the relative change in *Vc* in group I (*above*) and group II (*below*). Pretreatment values are 100%. $^{**}P < 0.025$; $^{****}P < 0.0025$

During bleomycin treatment no changes in TlCO were found in group I, but thereafter TlCO decreased significantly from week 30 onward ($P < 0.025$), while the values at the end of the study period were still lower than the initial values ($P < 0.005$). In group II the TlCO was already significantly decreased at week 12 ($P < 0.0025$), while at the end of the study period the values of TlCO were still lower than the initial values ($P < 0.025$) (Fig. 1).

No changes in *VA* were found during or after therapy in group I, but in group II a decrease in *VA* at the end of the therapy was measured ($P < 0.0025$), with total recovery at the end of the study (Fig. 2).

In group I, *Dm* was significantly decreased ($P < 0.0025$) at the end of remission-induction therapy; this decrease persisted till the end of the study ($P < 0.0025$). The same changes were observed in group II, with a reduction at 12 weeks ($P < 0.0025$) and at the end of follow-up ($P < 0.0025$) (Fig. 3).

Vc decreased in group I during therapy ($P < 0.0025$), with recovery during follow-up to values comparable with the initial values (n.s.). In group II the same tendency was suggested during treatment, but could not be proven significant. After discontinuation of the bleomycin treatment there was a tendency for values to increase (Fig. 4).

Because the bleomycin dose was fixed and not based on the body surface area, the total cumulative dose given was recalculated for body surface area for each individual patient. Changes in the lung function parameters related to the cumulative dose did not significantly differ from those related to the cumulative dose per body surface area.

Discussion

In this study we have evaluated the changes in slow vital capacity, transfer factor for CO, membrane factor, and capillary volume in a homogeneous group of patients with disseminated testicular carcinoma treated with *cis*DDP, vinblastine, and bleomycin [8].

We could not confirm the results of Comis et al. [6], who found TlCO the most sensitive parameter in monitoring subclinical bleomycin-induced pulmonary toxicity. We found no change in TlCO in group I during and after the therapy. However, we found *Vc* and *Dm*, as the components of the TlCO, to be more sensitive for diagnosis of subclinical pulmonary toxicity.

The decrease in *Vc* may be the result of a toxic effect of bleomycin on pulmonary vasculature. This hypothesis is supported by histopathological studies. Adamson and Bowden demonstrated that the first damage caused by bleomycin was localized in the endothelium of the pulmonary vasculature [1]. Moreover, bleomycin can also lead to clinical vascular diseases, such as Raynaud's phenomenon and coronary artery disease [15, 16].

In animal studies the initial injury to pulmonary endothelium was found to be followed by intra-alveolar and septal fibrosis, progressing in severity and finally involving the entire lung [4].

It is possible that damage to the pulmonary capillary vasculature is reflected in a decrease in *Vc*. This damage appears even during remission-induction therapy.

At the end of the therapy the membrane factor *Dm* decreases. There is some evidence [3] that *Dm* does not reflect the true diffusion capacity of the alveolar capillary membrane. However, *Dm* can be considered the physical component of the resistance to diffusion. *Dm* might therefore be the functional expression of interstitial fibrosis. This decrease in *Dm* is also larger in the group developing BIP, and persists in both groups until at least a year after therapy.

After therapy *Vc* increased gradually in both groups. This might be due to the recruitment of other capillaries in the lung. Such a recruitment could serve as a functional compensation for the reduced *Dm*. Thus, the result of this compensation would be a smaller decrease in TlCO.

The decrease of *VC* and *VA* in the group of patients developing BIP is probably related to interstitial and alveolar edema and inflammation. The recovery of *VC* and *VA* at the end of the observation period could be explained by the disappearance of the inflammatory reaction.

In conclusion, we suggest that the subclinical vascular damage of the capillaries of the lungs caused by bleomycin can be measured with *Vc*, and that the ensuing fibrosis can be monitored with *Dm*. TlCO seems to be a less valuable parameter of subclinical bleomycin-induced pulmonary toxicity during treatment and the decrease of TlCO after discontinuatioan of therapy can be explained by the continuing decrease of *Dm*. In those patients developing clinical toxicity, the decrease in TlCO is an expression of the decrease of *Dm* together with a compensating increase in *Vc*. Therefore, we advocate the use of *Vc* and *Dm* in monitoring bleomycin-induced pulmonary toxicity.

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