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FACTORS AFFECTING THE PULMONARY TOXICITY OF BLEOMYCIN

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Bleomycin is a glycopeptide antibiotic produced by Streptomyces verticillis. It consists of at least 7 polypeptides. The drug is most active in the G_2 phase of the cell cycle and has been shown to cause a scission of single stranded DNA (UMEZAWA 1973, LOWN & SIM 1977). Bleomycin has been effective particularly in the treatment of lymphomas, and vulval and testicular carcinomas (HOOGSTRATEN et coll. 1975, HAAS et coll. 1976). It has a wide range of toxicity, the lungs being most important target organs (DELENA et coll. 1972, BLUM et coll. 1973, CROOKE & BRADNER 1976, COLE 1977, COMIS 1978). The frequency of the side effects ranges from 5 to 40 per cent, while the mortality rate lies between 0 and 10 per cent (CATANE et coll. 1979). The lung toxicity has been analyzed by clinical (DELENA et coll.) and functional tests (COMIS et coll. 1979, LEWIS & IZBICKI 1980) and by histopathologic techniques (GEBBELS et coll. 1975). The toxicity may be related to the total dose of the drug, to the route of administration, and to the age of the patient.

In the present investigation, the effects of age and smoking, as well as of the dose and the route of administration, on the pulmonary toxicity of bleomycin were retrospectively analyzed.

Material and Methods

The material consisted of 62 patients treated at this hospital between 1968 and 1978. Those selected were free from any pre-existing pulmonary disease, and none of them had received drugs known to affect the lungs. The diagnoses appear in the Table. Group A includes patients with vulval malignancies and Group B patients with malignancies of the head and neck (20 males, 3 females). The mean age in group A was 69.8 years (range 29–89, SD 11.8) and in group B 60.6 years (range 32–76, SD 10.11). None of the patients in group A had previously smoked, while 19 patients in group B had smoked on average 20 cigarettes a day for about 40 years (range 15–56). Two patients in this group had never smoked, and no information was available for 2 patients.

Before bleomycin therapy, all patients were examined concerning size and spread of the tumor, total blood cell count, and creatinine clearance; routine liver function tests and chest radiography were also performed. During the treatment, platelet counts and white blood cell counts were determined 1 to 2 times weekly. The chest films were controlled weekly before the treatment and during therapy. After termination of the therapy, chest radiography was performed as a control every 2 or 3 months.

The patients in group A were treated with intravenous bleomycin (Lundbeck) once every 2 days, the dose being 15 to 30 mg (dissolved in 0.9% NaCl before use). The mean of the total dose was 211 mg (range 30–510, SD 122). The patients in group B were treated with intramuscular bleomycin every 2 days before external irradiation, except for one patient who received bleomycin by intraarterial infusion instead of intramuscular injection. In this group the single dose was 7.5 to 15 mg once every 2 days and the mean of the total dose was 117 mg (range 60–300, SD 64).

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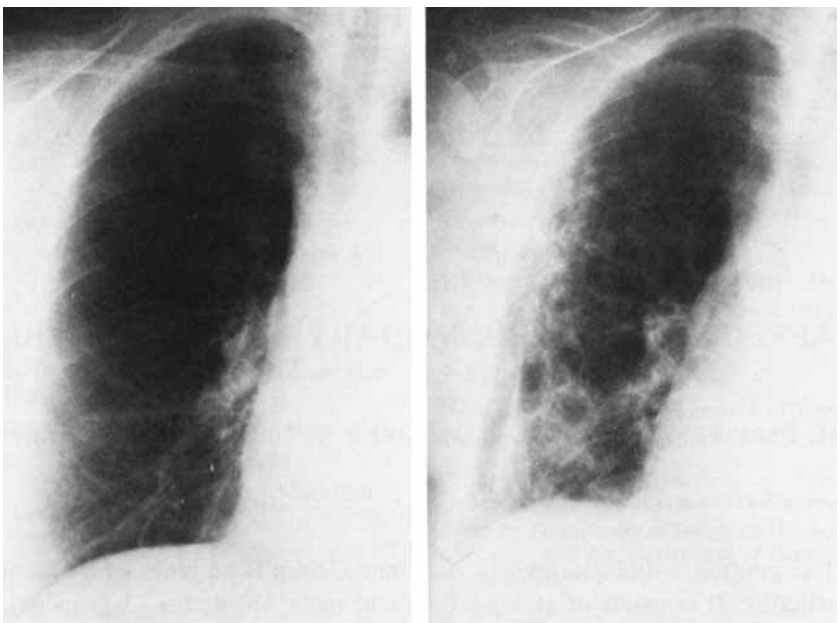


Fig. 1. Woman aged 76 years. a) Conventional chest roentgenogram before treatment. b) Thickening of the lateral pleura and parenchymal lesions 42 days after beginning of bleomycin therapy (total dose 240 mg).

Table

Primary site and histopathology of the tumors in groups A and B

Group	No. of patients	Site		Histopathology	
A	39	Vulva	39	Epidermoid carcinoma	37
				Malignant melanoma	2
B	23	Larynx	14	Epidermoid carcinoma	14
		Tongue	5	Epidermoid carcinoma	4
				Adenoid cystic carcinoma	1
		Oral mucosa	3	Epidermoid carcinoma	3
		Palatine tonsil	1	Epidermoid carcinoma	1
Total	62		62		62

Results

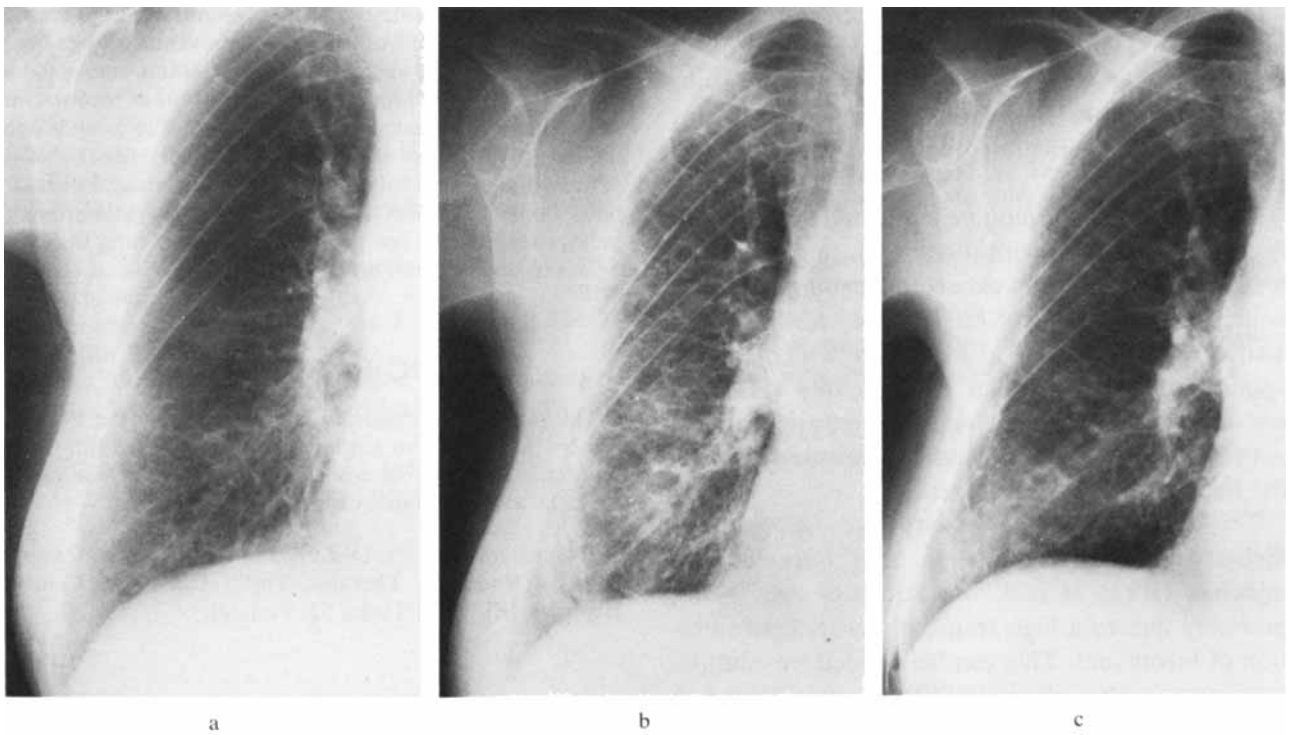
In group A, 6 out of 39 patients (15.4%) developed typical pulmonary fibrosis as seen in the chest films and in group B only 1 out of 23 patients (4.3%). Thus, the occurrence of pulmonary fibrosis in the whole material was 7 out of 62 patients (11.3%). In none of these cases was the pulmonary fibrosis lethal.

The mean age in group A (69.8 years) differed significantly ($p<0.005$) from that in group B (60.6 years). In group A, the mean age was 68.8±8.0 for patients with pulmonary fibrosis and 70.0±12.3 for those without pulmonary fibrosis; the difference was not significant.

The mean total bleomycin dose in group A (211±122 mg) differed significantly ($p<0.005$) from that of group B (118±64 mg).

In group A, the mean total bleomycin dose was 286±128 mg for patients with pulmonary fibrosis and 197±119 mg for those without pulmonary fibrosis; the difference was not significant ($p=0.2$).

In group B, the bleomycin dose for the patients with pulmonary fibrosis was 300 mg, which differed significantly from the mean dose for the other pa-



a b c

Fig. 2. Woman aged 68 years. a) Conventional chest roentgenogram before treatment. b) Thickening of the laterobasal pleura and some parenchymal lesions 73 days after beginning of bleomycin therapy (total dose 300 mg). c) One year after cessation of bleomycin. Roentgenologic regression but small well demarcated, fibrotic parenchymal lesions still visible.

tients in that group ($p<0.02$). The patient with pulmonary fibrosis in group B was a 67 year old, previously healthy man, who had smoked on average 20 cigarettes a day for 35 years. He suffered from a tonsillar epidermoid carcinoma.

No differences in the radiologic appearance of the lung fibrosis were noted between groups A and B. Pleuritis with exudate in the laterobasal pleural cavity with thickening of the pleura was the first symptom, followed by development of fibrotic alterations in the lung parenchyma adjacent to the pulmonal pleura (Figs 1, 2). This might have been caused by accumulations of alveolar and interstitial exudate. These alterations were usually seen first in the right lung, and only in severe cases were they apparent in both lungs.

No abnormal findings were noted in blood tests taken during the bleomycin treatment, and no allergic or other skin reactions occurred. In a few patients the treatment was withdrawn because of general exhaustion or intensive mucosal lesions in the oral cavity.

Discussion

The mechanism of development and the histopathology of bleomycin induced lung fibrosis have been investigated in some detail (GEBBELS et coll., MCCULLOUGH et coll. 1978, SICIC et coll. 1978). The histopathologic manifestations of bleomycin lung toxicity in man are similar to those in interstitial pneumonitis and fibrosis caused by several other lung toxins.

For the diagnosis of bleomycin induced lung toxicity, the clinical and radiographic findings are the most important. Several tests have been suggested for the early detection of lung toxicity (RICHMAN et coll. 1975, COMIS et coll.). The pulmonary function test may be inaccurate and misleading, however (LEWIS & IZBICKI).

The incidence of bleomycin induced lung toxicity has been reported to vary between 5 and 40 per cent (COMIS), which is in accordance with the present observations (11.3%).

The radiologic findings in this series were similar to those published earlier. However, the observation that the alterations usually appear first in the right lung has not been previously reported. As the alterations sometimes appeared rapidly, within one week after inception of therapy, frequent controls were important.

BONADONNA et coll. (1972) found that the incidence of bleomycin induced lung toxicity increased

after 50 years of age, whereas others reported an increase first after the age of 70 years (BLUM et coll., HAAS et coll., COMIS). The present results support the latter findings: the incidence of lung toxicity was significantly higher in the older age group.

The frequency of bleomycin induced lung toxicity is clearly correlated with the total dose of the drug; it increases after doses exceeding 200 mg (BLUM et coll., CROOKE & BRADNER, HAAS et coll.). This is also considered to be a dose after which the response of the tumor can be evaluated (HAAS et coll.). Higher doses are indicated only in patients with responsive tumors. This is also supported by the findings in the present series.

The frequency of lung toxicity is considered to be higher after intravenous than after intramuscular injection (HAAS et coll., RYGÅRDH et coll. 1976), probably due to a high transient serum concentration of bleomycin. This can be avoided by continuous intravascular infusion of bleomycin (COOPER & HONG 1981). In the present series, the frequency of lung fibrosis was higher after bolus intravenous bleomycin than after intramuscular bleomycin, although the difference may also have been caused by the different mean ages of the patients.

Severe cases of bleomycin induced lung fibrosis have been claimed to be associated with smoking (HAAS et coll.). In the present series, most patients in group B could be regarded as heavy smokers, while group A only contained non-smokers. Obviously the frequency of lung fibrosis was not increased by heavy smoking at bleomycin levels below 200 mg.

It therefore seems obvious that bleomycin induced lung fibrosis is primarily related to the cumulative total dose of the drug, which should exceed 200 mg only in patients with responsive tumors. These patients should be kept under observation, with frequent chest radiography, particularly when they are over 70. The results also suggest that intramuscular administration or intravascular infusions give less lung toxicity than intravenous injections. Smoking, or the sex of the patient, seemed to have only minor influences on bleomycin induced lung toxicity.

SUMMARY

Bleomycin induced lung toxicity was retrospectively analyzed in 39 patients with vulval malignancy (group A) and in 23 patients with head and neck carcinoma (group B). Group A consisted of non-smokers, mean age 69.8 years, who received the drug as intravenous injections. Group B contained mainly heavy smokers, mean age 60.6 years, treated with intramuscular injections of bleomycin. In group A, 6 patients (15.4%) and in group B only one patient (4.3%) developed typical pulmonary fibrosis. Advanced age, a high total dose of bleomycin, and intravenous bolus injections of the drug seemed to be major factors responsible for the development of lung fibrosis, whereas smoking had no obvious effect.

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