Pulmonary changes induced by bleomycin

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SUMMARY

Bleomycin is an antitumor antibiotic, which is used among others in the treatment of patients with disseminated testicular cancer. Its lack of myelosuppression makes bleomycin appropriate for combination chemotherapy schedules. The dose-limiting side effect of bleomycin is the pulmonary toxicity.

Because of the improved results in the treatment of patients with disseminated testicular cancer, the quality of life of these patients is to an important degree determined by the side effects of the cytostatic drugs. Studies of these side effects are therefore relevant.

The studies, described in this thesis, were carried out in a group of patients with disseminated testicular cancer. All patients were treated with bleomycin for 12 weeks, in a dosage of 30 mg once a week, injected intravenously, and two other cytostatic drugs without pulmonary toxicity, namely cis-diammine-dichloro platinum and vinblastine.

The following questions were formulated in chapter I:

1. What is the value of pulmonary function tests in detecting and monitoring (sub-)clinical bleomycin toxicity?
2. What influence does renal function have on the pulmonary toxicity of bleomycin?
3. Is it possible to predict the occurrence of bleomycin-induced pneumonitis (BIP)?
4. What is the meaning of a decreased pretreatment value of the spirometry, the transfer factor of the lungs for carbon monoxyde (TlCO) and its components?
5. Is there a degree of reversibility of the bleomycin-induced changes in lung function parameters?

A review of the literature concerning bleomycin is given in chapter II. It is known that bleomycin can induce an interstitial pneumonitis in animals and men. Investigations into the role several examinations play in the detection and monitoring of the bleomycin-induced damage are discussed. Risk factors in the occurrence of BIP are given. Results of investigations into the prevention and treatment of BIP and bleomycin analogues are also discussed.

In chapter III the lung function tests, used in all studies, are described.

In chapter IV the changes in spirometry, TlCO, the diffusing capacity of the alveolo-capillary membrane (Dm) and the pulmonary capillary blood volume (Vc) are described. Two groups of patients could be discriminated. One group without (I) and one group with (II) clinical signs and symptoms of BIP. It was found that no changes in the slow inspiratory vital capacity (VC) and VA were present in group I during the remission induction of twelve weeks and the ensuing observation period of 42 weeks. In this group TlCO decreased in the second part of the observation period. The same was found in Dm, but to a greater degree. Vc decreased during the remission induction, but returned to pretreatment values in the observation period in this group. We found a decrease in VC and VA, that disappeared during the follow-up period. The decrease of TlCO and Dm started earlier and occurred to a greater degree in group II. The decrease of Vc was less pronounced in this group, but the increase of Vc above the pretreatment value during the observation period was striking.

These results demonstrate TlCO to be less sensitive in monitoring bleomycin-induced pulmonary toxicity than its two components Dm and Vc. It is suggested that the initial endothelial damage may be expressed by the decrease of Vc and the ensuing fibrosis can possibly be measured by Dm. The increase of Vc may act as a compensation mechanism for the reduced Dm, and in this way to a smaller reduction of TlCO.

In chapter V the relationship between renal function and pulmonary function is described. This investigation was carried out because the CDDP can lead to a decrease of renal function and in this way to a decreased clearance of bleomycin which can possibly cause an increased risk of pulmonary toxicity. The glomerular filtration rate (GFR), the effective renal plasma flow (ERPF), the spirometry and the TlCO were measured before the start of any therapy and at the end of the remission induction in 18 patients. A relationship between the change in GFR and the change in TlCO was found. No relationship could be demonstrated between the other investigated parameters. It was concluded that a CDDP-induced renal function impairment increases the risk of bleomycin-induced pulmonary toxicity.

The results of the investigation carried out to demonstrate which parameters are valuable in predicting BIP are described in chapter VI. Spirometry, TlCO, Dm, Vc and creatinine clearance were measured in 39 patients. Eight of these 39 patients developed BIP. After performing

discriminate analysis, it was concluded that patients with a low-normal creatinine clearance in combination with a decrease in VC and VA, without a change of Vc run an increased risk of developing BIP. It is advised to monitor these parameters during therapy.

The meaning of an abnormal pretreatment TlCO, Dm or Vc is described in chapter VII. It was found that a subgroup of patients with a low Vc could be discriminated before the start of the therapy. There were no differences anymore between this subgroup and the other patients at the end of the study period. The risk of BIP was not increased in the patients with a decreased pretreatment Vc, therefore no reduction of the dose of bleomycin seemed indicated in this subgroup. This decreased pretreatment Vc can possibly be explained by tumor embolism.

The natural course of BIP is described in chapter VIII. It was found that patients had no pulmonary signs and symptoms two years after BIP. Chest radiographs also showed no abnormalities anymore. Pulmonary function tests had all normalised. Other investigations such as technetium perfusion scan and Xenon ventilation perfusion scan similarly showed no abnormalities two years after BIP. The broncho-alveolar lavage (BAL) was performed to find out if different forms of BIP could be demonstrated. BAL was carried out in three patients when they were suffering from BIP and showed divergent changes in the differentiation of the total cell amount. It can be concluded that there is a complete reversibility of all parameters in patients with BIP and that the value of BAL is unclear, but that further investigations are indicated.