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Local therapy of malignant pleural effusion with mitoxantrone

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Twelve patients received intrapleural instilments of the cytostatic agent mitoxantrone in a total dosage of 30 mg for locoregional palliative therapy of malignant pleural effusion. Effusion could be stopped for a mean period of 3.2 months in 11 patients.

Key words: Locoregional chemotherapy, malignant pleural effusion, mitoxantrone, palliative therapy, pleurodesis.

Introduction

Malignant pleural effusion is a frequent complication of cancer with an estimated incidence of 15 000 cases yearly in Germany. Approximately 25–49% of breast cancer patients and 6–17% of patients with ovarian cancer develop this condition,[1] which is a major therapeutic problem due to fast recurrence and considerable restrictions on the patient's life.

In recent years, pleurodesis in combination with local instillation of various drugs, as opposed to relief puncture alone, has regained importance. This treatment was shown to either totally prevent recurrence or at least considerably extend intervals between punctures,[1,2] an important point, as cavitation and callus formation increase with each recurrence.

Since only a small number of malignant pleural effusions respond to systemic chemotherapy, the aim of treatment is pain relief. Advantages of intracavitary tumor therapy alone are (1) high local concentrations of cytotoxic agents and (2) reduction of systemic side effects. This has been demonstrated repeatedly in proliferation assays with monolayer cell cultures and by pharmakokinetic evaluation.[3–5]

During recent years, the cytostatic agent mitoxantrone (1,4-dihydroxy-5,8-bis[(2-(2-hydroxyethyl)amino)ethyl)amino)]-9,10-anthracenedione dihydrochloride) has been used increasingly in locoregional therapy for the following reasons. (1) Due to its high polarity and protein binding, the substance is absorbed extremely slowly from the serous cavities. Long-term concentrations in the pleural cavity are therefore 100- to 200-fold higher than after i.v. injection.[6,7] (2) Pharmakokinetic studies show that only 17% of the total dosage reaches the circulation after intrapleural administration.[3]

Method

Patient population

Eight patients with breast cancer, three with ovarian cancer and one patient with pancreatic carcinoma were studied. All pleura specimens taken during treatment were examined cytologically to detect malignant cells. Only one patient had been submitted to unsuccessful pleurodesis treatment 3 weeks before. Systemic therapy had been performed at least 4 weeks before the beginning of the study.

Treatment

Treatment was started by complete drainage of the effusion via a pleural catheter of small caliber. The pleural fluid was drained spontaneously to avoid possible complications of forced drainage, e.g. pulmonary edema or homeostatic circulatory disorders. To prevent pleuralgia, which is frequency associated with tetracycline pleurodesis, we instilled 5 ml 2% xylocaine and, additionally, 15 ml containing 30 mg mitoxantrone as a prophylactic measure. The catheter was subsequently rinsed with 20 ml physiologic saline solution. Following instillation, the catheter was removed for 24 h and then reconnected for permanent drainage. If less

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than 200 ml was drained, the catheter was removed. If the residual fluid was more than 200 ml, this was drained and instillation repeated in the same way, followed by immediate removal of the catheter. A chest X-ray was performed directly afterwards. Follow-up examinations were performed 4 and 12 weeks, and 6, 9 and 12 months after pleurodesis.

Results

The following results were obtained.

(1) Despite xylocaine administration, seven of the 12 patients reported pain during the 24 h of mitoxantrone retention in the intrapleural space. In one case the cytostatic agent had to be drained after only 1.5 h, as even dipidolor did not have the desired analgesic effect. In retrospect, this may be explained by the injection time of clearly less than 10 min in all these patients.

(2) Drainage volumes of pleural effusions were between 400 and 3500 ml (mean: 1700 ml).

(3) Only one patient had recurrent pleural effusion within 4 weeks. Follow-up was between 4 weeks and 12 months. Effusion was stopped completely for at least 3 months in 11 patients.

(4) In 11 cases, X-rays revealed callus formation in the pleural membrane; an intracavitary recurrence was found in only one case.

(5) Three patients developed WHO grade II leukopenia on the 10th day after injection.

Discussion

Although our local therapy cannot cure the underlying diseases, we achieved a durable response and clearly improved respiration for a mean of 3.2 months in our patients. Thus, the recurrence-free interval corresponded to that of tetracycline pleurodesis, after which a mean of 50% of patients within 12 weeks had recurrent effusions requiring drainage.[8] Although, according to other studies, only 17% of the locally administered dosage reaches the circulation,[1] 25% of our patients developed WHO grade II leukopenia[9] on the 10th day after injection of the total dose of 30 mg mitoxantrone. Thus, parallel systemic administration of other cytostatic agents is not advisable. However, due to the relatively short recurrence-free intervals, an increase of the total dosage may be worth considering for this type of local therapy.

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