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Management of peritoneal effusions with intracavitary mitoxantrone or bleomycin

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Peritoneal effusion is a common complication in disseminated cancer. Intracavitary instillation of various agents has achieved control rates of 30–60% with no rational preference for one agent or another. However, serious side effects have also been observed and deaths due, for instance, to bleomycin have been reported. Mitoxantrone has recently been tested to treat effusions, and preliminary results suggest the high efficacy of this drug in the treatment of peritoneal, pericardial and pleural effusions. Nevertheless, some results have been conflicting. In the present study, 41 patients with peritoneal effusions were treated with intracavitary bleomycin or intracavitary mitoxantrone. The median duration of control of effusion was 5 months (range 1 week to 14 months) with mitoxantrone and 4 months (range 1 week to 12 months) with bleomycin. We conclude that, taking into account their limitations, both agents can be used successfully in the treatment of peritoneal effusions.

Key words: Bleomycin, mitoxantrone, peritoneal effusion.

Introduction

Peritoneal effusion is a common complication in many advanced cancers and almost half of the patients with advanced breast or lung cancer have either pleural or peritoneal effusion. In some cancers, the prognosis is even related to the presence or absence of effusion.[1,2] Peritoneal effusion has a poorer prognosis than pleural effusion.[2] Thus eradication of the complication might significantly improve the patient's quality of life. It has also been suggested that intraperitoneal administration of antineoplastic agents might have a tumoricidal effect with minimal systemic adverse effects.[3] Drainage of intraperitoneal effusion alone could be used, but the procedure must be repeated frequently. Such treatment definitely increases the risk of infection and other complications, peritonitis among them. The procedure also causes pain and other discomfort. Continuous drainage of the peritoneal effusion and intracavitary use of sclerosing agents or cytostatics, such as bleomycin, have been almost routine practice during the past decade, achieving high permanent control rates. The most common side effect of intracavitary bleomycin has been fever in almost 20% of the patients reviewed.[4] Death possibly related to intracavitary bleomycin has also been reported in six (17%) of 35 patients with malignant pleural effusion.[5–7] The mechanism of bleomycin toxicity has still not been clearly established, but pharmacokinetic methods have demonstrated that almost 40% of intracavitary bleomycin is absorbed in the system. It has therefore been suggested that intracavitary doses of bleomycin should not exceed 40 mg/m^2.[5–8] According to reports in the literature, the recurrence of peritoneal effusion after bleomycin has ranged between 40 and 70%.[4,9,10]

Mitoxantrone is a relatively recent antineoplastic agent, an anthracenedione derivative that has proved efficacious in patients with breast cancer, malignant lymphomas and leukaemia.[8,11,12] Intraperitoneal mitoxantrone has been found efficacious in intra-abdominal or pelvic tumor masses.[12] Associated with its high tissue-binding properties and high therapeutic index, it has also recently demonstrated potentially high efficacy in the treatment of effusions.[3,13]

It has been shown that mitoxantrone is sequestered in the intraperitoneal space and slowly released. Four weeks after treatment, high plasma concentrations of mitoxantrone were measured, indicating that it was still being released in an active form.[3,11]

Doses of 30 mg/m^2 intracavitary mitoxantrone have been recommended on the basis of pharmacokinetic studies.[3] Nevertheless, the toxicity of the agent has been considered a dose limiting factor. Severe leukopenia has been observed in four of 21 patients receiving a dose of mitoxantrone higher than 35 mg/m^2.[3] Intraperitoneal mitoxantrone could be repeated every 2–3 weeks without severe toxicity.[3] In our previous study with pleural effusions, 30 mg of intracavitary mitoxantrone did not show severe toxicity.[16] In the light of the above

findings, however, it was decided that the dose of mitoxantrone used in the heavily pretreated patients of this study should not exceed 20 mg/m^2. The first reported results on its efficacy in peritoneal effusions were conflicting.[14,15]

The purpose of the present study was to establish which agent (bleomycin or mitoxantrone) should be used in the treatment of peritoneal effusions to improve the quality of life in properly selected patients by achieving more permanent responses with fewer adverse effects.

Patients and methods

Patients

Forty one patients (16 men and 25 women) with symptomatic peritoneal effusions due to malignant disease were treated with intracavitary bleomycin (18 patients) or mitoxantrone (23 patients). The most common symptoms were abdominal tenseness, dyspnoea, discomfort and abdominal pain. The mean age was 58 (range 32–76) years with no difference in age between the groups. All patients were heavily pretreated with anticancer chemotherapy for clinical stage IV disease.

In this open label phase II study, patients with myelosupression or known allergy to mitoxantrone or anthracyclines, and patients previously treated with systematic mitoxantrone received intracavitary bleomycin. Otherwise, they were treated with intracavitary mitoxantrone. Patients with carcinosis or with other changes in the lungs imparing respiratory performance were also put on the mitoxantrone regimen.

Methods

Peritoneostomy and tube drainage were performed. Drainage did not exceed 3000 ml/day but was as complete as possible as confirmed by diminution of effusion. After theoretically complete drainage, either 60 mg of bleomycin in 100 ml physiological saline or 30 mg of mitoxantrone in 30 ml physiological saline was instilled into the abdominal cavity. The peritoneostomy tube was then closed for 24 h, allowing theoretical action of the drug used.

The peritoneostomy tube was then opened and drainage was continued until the end of effusion or the manifestation of a side effect or symptoms (e.g. infection) requiring interruption of the procedure.

Evaluation of results

The results were evaluated on the basis of subjective (alleviation of symptoms and Karnofsky index[17] and objective (response to intracavitary chemotherapy) findings. An improvement in the Karnofsky index of more than 30% was considered a significant change. Blood counts were performed before, during and after the treatment. Cytological analyses were carried out in all cases. Leukopenia was evaluated according to WHO graduation.[18]

Because there are no standard criteria on which to assess the response to treatment in peritoneal effusions, the duration of control of effusion was considered as objective response criteria.

Results

Cytological confirmation of malignant effusion was confirmed in all patients.

Subjective findings

Tenseness, dyspnoea and abdominal pain decreased in all patients. The total effusion volume varied between 8 and 22 l. After instillation of bleomycin or mitoxantrone, the total volume of effusion varied between 1.3 and 3 l. The Karnofsky index improved in 18 (78%) of patients treated with mitoxantrone and in 11 (61%) of those treated with bleomycin.

Objective findings

The median duration of control with mitoxantrone was 5 months (range 1 week to 14 months) and 4 months (range 1 week to 12 months) with bleomycin. Highest control rates of effusion were achieved with mitoxantrone or bleomycin in patients with malignant lymphoma and those with breast cancer.

Adverse effects

Leukopenia (WHO grades 2 and 3) was observed in 26% of the patients receiving mitoxantrone and microbiologically documented infection in 35% of the patients (Table 1). All infections were caused by Gram-positive microorganisms; *Staphylococcus aureus* in one patient, *S. epidermidis* in six patients and *Streptococcus agalactiae* in one patient. Fever

Table 1. Adverse events during intracavitary treatment of peritoneal effusion with mitoxantrone or bleomycin

Side effect	Treatment	
	mitoxantrone [*N* = 23 (100%)]	bleomycin [*N* = 18 (100%)]
Fever	—	5 (28%)
Leukopenia	6 (26%)	—
Abdominal pain	5 (22%)	—
Nausea/vomiting	2 (9%)	1 (6%)
Microbiologically documented infection	8 (35%)	1 (6%)
Allergy	—	2 (11%)

was induced by bleomycin in 28% of the patients. Other adverse effects are listed in Table 1.

Discussion

Problems have been encountered with reporting the results achieved in the treatment of peritoneal effusions. These discrepancies are mainly due to differences in the treatment methods used and to differences in the evaluation criteria of the results obtained. Subjective and objective findings are generally interpreted differently, as is the duration of responses.

Intracavitary use of various agents becomes necessary when systemic chemotherapy fails in the treatment of peritoneal effusions. Control of peritoneal effusions is rarely permanent in patients with advanced cancer, so the primary aim of the treatment was to improve the quality of life of such patients. Thus far, bleomycin has been considered the most effective agent. Control of peritoneal effusions has been achieved in almost 60% of the patients receiving this agent intracavitarily.[4,9,10] Failure has usually occurred in patients with a rapidly progressing disease.[4]

The use of mitoxantrone to treat effusions is relatively recent and there have been contradictory reports concerning its efficacy. For instance, no significant difference was seen when mitoxantrone was compared with a placebo in the treatment of pleural effusions.[3,14]

In the present study, mitoxantrone was quite well tolerated and could be safely administered but it causes much more adverse events than bleomycin. For instance, there was no death due to mitoxantrone but grades 2 and 3 leukopenia were present in 26% of the patients, and 35% developed infection. All these patients have previously been heavily treated with antineoplastic chemotherapy and already had grade 1 leukopenia.

Because mitoxantrone causes bone marrow depression, it should be used sparingly in patients with severe leukopenia or in those simultaneously receiving systemic chemotherapy.

In the present study, both mitoxantrone and bleomycin were efficacious against malignant peritoneal effusions. All patients received the same dosage regardless of their body surface. Nevertheless, an increase in toxicity in smaller patients or decreased efficacy in larger patients could not be reliably established. According to Paladine *et al.*,[4] toxicity and tolerance from bleomycin were not dose related, and toxic manifestations did not predict the results. In the present study, the best results with mitoxantrone were achieved in patients with breast cancer and malignant lymphoma. Effusions caused by malignant disease of the gastro-intestinal tract and cancers of unknown primary were poorly controlled. Not all those who responded to intracavitary treatment improved subjectively nor did the Karnofsky index increase in all patients. The most common reasons for poor subjective response were carcinosis of both lungs, the presence of infection and a poor general condition caused by metastases in other sites.

Bleomycin was well tolerated, but 28% of the patients developed fever requiring indomethacin. Bleomycin did not cause myelosupression and in the present study there was only one case of infection among patients receiving intracavitary bleomycin. This agent should be preferred for patients with neutropenia or for those not responding to mitoxantrone.

It has been reported that almost 40% of intracavitary bleomycin is absorbed into the system.[5,6] Mitoxantrone should therefore be preferred to bleomycin for patients with changes in lungs imparing respiratory performance and also for patients pretreated with bleomycin who are at risk of pneumonitis or fibrotic changes. In order to achieve higher and permanent control rates, larger doses of mitoxantrone or bleomycin could be used but the side effects could then be more severe in such heavily pretreated patients.

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