

Clinical Research

Intrapericardial Cisplatin Administration after Pericardiocentesis in Patients with Lung Adenocarcinoma and Malignant Cardiac Tamponade

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Introduction: Patients with lung adenocarcinoma often suffer from metastatic pericardial effusion that may eventually cause cardiac tamponade. Recurrence of pericardial effusion is frequent after pericardial drainage and therapy for the prevention of fluid reaccumulation is still controversial. We evaluated the safety and effectiveness of the intrapericardial infusion of cisplatin, a substance with antineoplastic and sclerosing properties, after pericardiocentesis in patients with lung adenocarcinoma and malignant cardiac tamponade.

Methods: Twenty-five patients (19 males and 6 females, median age 55 years) with lung adenocarcinoma confirmed by cytological examination and cardiac tamponade were studied. All patients underwent sub-xiphoid pericardiocentesis through catheter insertion, under electrocardiographic, echocardiographic and haemodynamic guidance. After the malignant aetiology of the pericardial effusion had been confirmed by cytological examination, cisplatin was instilled (10 mg in 20 ml normal saline) into the pericardial cavity during three consecutive days. Clinical and echocardiographic evaluation was performed every month thereafter.

Results: Pericardial fluid of 350-1700 ml was removed (median 750 ml) and was haemorrhagic in 80% of the cases. Paroxysmal atrial fibrillation was detected in three patients (12%) and non-sustained ventricular tachycardia in two (8%). None of the patients had hypotension or retrosternal pain. One patient suffered from significant pericardial effusion reaccumulation (4%). Laboratory findings were not influenced by systemic drug absorption in any patient. Transthoracic echocardiographic study revealed pericardial thickening without physiology of constriction in 4 patients (16%). After pericardiocentesis, the mean survival period overall was 4.5 months (range 3-92 weeks), and mortality was attributed to widespread disease (respiratory failure).

Conclusions: Intrapericardial administration of cisplatin is safe and effective in preventing the reaccumulation of malignant pericardial effusion in the majority of patients with lung adenocarcinoma.

Malignant involvement of the heart and/or pericardium is not uncommon in patients with advanced cancer (10%) and is involved in the mechanism of mortality in one third of cases.¹ The most common primary tumour invading the pericardium is lung cancer, followed by breast cancer, melanoma, Hodgkin's and non-Hodgkin's lymphoma and leukaemia.^{2,3} Metastatic involvement of the heart or peri-

cardium may occur either from direct invasion by an adjacent primary tumour or by lymphatic or haematogenous spread. In the majority of patients with lung cancer, hilar lymphatic drainage is responsible for pericardial effusion.⁴ Increase in pericardial fluid may cause life-threatening cardiac tamponade in patients with satisfactory survival prospects. The acute treatment of malignant cardiac tamponade involves prompt

complete removal of pericardial fluid, by pericardiocentesis or surgical intervention (pericardial fenestration). Recurrence of malignant pericardial effusion and subsequently tamponade is extremely frequent (40-70%).¹⁻⁴ Therapeutic strategies remain controversial depending on the experience of each individual centre. It may be managed by the intrapericardial infusion of sclerosing agents, intracavity and/or systemic chemotherapy, radiation therapy or surgical intervention.⁵⁻⁹

In our study we chose cisplatin instillation as the method for preventing recurrence of malignant pericardial effusion in patients with lung adenocarcinoma for the following reasons:

- although lung adenocarcinoma is a fairly drug-refractory neoplasm, cisplatin is one of the preferred chemotherapeutic drugs for that particular tumour,¹⁰
- it causes mild pericardial sclerosis^{11,12} and
- laborious surgical intervention (thoracotomy, pericardial window formation) is avoided in critically ill patients.

Methods

Patients

Between 1999 and 2004 the diagnosis of cardiac tamponade was made in a total of 60 patients with large pericardial effusion (diastolic diameter of epicardial-pericardial separation exceeded 10 mm, measured behind the left ventricle at the level of the tips of the mitral valve). The clinical criteria for the diagnosis of cardiac tamponade were considered to be the following: pulsus paradoxus >12 mmHg, central venous pressure >10 mmHg, and hypotension (systolic arterial pressure <100 mmHg).¹³ All patients underwent two-dimensional and M-mode echocardiography for the detection of pericardial effusion and the presence of constriction of the right cardiac cavities.¹⁴⁻¹⁶

The primary tumour was lung cancer (39 patients), breast cancer (11 patients), urinogenital (3 patients), lymphoma (2 patients), leukaemia (2 patients), stomach cancer (1 patient), mesothelioma (1 patient) and malignant melanoma (1 patient). Of the 39 patients with lung cancer, according to histological examination, 25 suffered from adenocarcinoma, 8 from non-small cell lung cancer and 6 patients from small cell lung cancer. Twenty-five patients, 19 male and 6 female, median age 55 years, with lung adenocarcinoma and cardiac tamponade were selected for intracavity cisplatin infusion because of the chemosensitivity of this histological type. The patients included in the stu-

dy scored 30 - 40 on the Karnofsky Performance Status Scale.¹⁷

Pericardiocentesis. Intracavity and systemic chemotherapy

After the diagnosis of cardiac tamponade was confirmed, the patients were admitted to the intensive care unit, where they underwent subxiphoid pericardiocentesis under electrocardiographic, echocardiographic and haemodynamic guidance (sedated with 2-3 mg midazolam). Penetration into the pericardial sac was performed with the patient positioned so that his chest was at a 45 degree angle, using a soft, multihole, J shaped 7F catheter (Seldinger technique). The catheter remained in the pericardial cavity for 6-10 days. After the malignant aetiology of the pericardial fluid was confirmed by cytological examination, cisplatin was instilled (10 mg in 20 ml of normal saline), administered over 5 min during three consecutive days directly into the pericardial space. Cisplatin was delivered to the most empty pericardial sac. After relief of cardiac tamponade, systemic chemotherapy was administered periodically to those patients who had no contraindications, using a combination regimen of paclitaxel-cisplatin. Clinical and echocardiographic evaluation was performed after cisplatin infusion and repeated every month thereafter. Treatment was considered successful when no recurrence of symptoms of large malignant pericardial effusion was observed in repeated examinations. The survival period was calculated from the day of pericardiocentesis to the date of death or the last clinical evaluation.

Equipment

A Caris echocardiograph (Esaote Biomedica) and a Sony UP-895CE recording device were used. For the pericardiocentesis and drainage we used the PeriVac system (Boston Scientific Technologies).

Results

Table 1 shows the symptoms and clinical signs of 25 patients with pulmonary adenocarcinoma and cardiac tamponade. Table 2 shows the main electrocardiographic, radiological and echocardiographic findings from the patients of the study.

After pericardiocentesis was performed and complete pericardial drainage was achieved, a total of 350-1700 ml (median 750 ml) pericardial fluid was removed

Table 1. Symptoms and signs from 25 patients with pulmonary adenocarcinoma and cardiac tamponade.

Symptoms	Patients	Signs	Patients
Dyspnoea	24 (96%)	Pulsus paradoxus	21 (84%)
Orthopnoea	19 (76%)	Tachycardia (>110/min)	17 (68%)
Cough	14 (56%)	Jugular venous distension	16 (64%)
Chest pain	13 (52%)	Diminished heart sounds	14 (56%)
Peripheral oedema	11 (44%)	Hypotension	12 (48%)
Facial oedema	9 (38%)	Hepatomegaly	10 (40%)
Haemoptysis	5 (20%)	Kussmaul sign	8 (32%)
Syncope	3 (12%)	Pericardial rub	4 (16%)

Table 2. Main electrocardiographic, radiological and echocardiographic findings from the patients of the study.

Findings	Patients
Electrocardiography	
1. low QRS voltage	21 (84%)
2. repolarisation abnormalities	20 (80%)
3. electrical alternans	18 (72%)
4. atrial fibrillation / flutter	6 (24%)
5. ST-segment elevation	3 (12%)
Chest X-ray	
1. enlarged cardiopericardial silhouette >0.5	23 (92%)
2. pleural effusion	16 (64%)
3. neoplastic lung infiltration	15 (60%)
Echocardiography	
1. large pericardial effusion (>1.0 cm)	25 (100%)
2. diastolic right atrial collapse	24 (96%)
3. diastolic right ventricular free wall collapse	23 (92%)
4. intrapericardial “tumour-shaped” infiltrations	12 (48%)

from the pericardial sac, leading to immediate relief of symptoms and signs of cardiac tamponade in all patients. Figures 1 and 2 show echocardiographic images

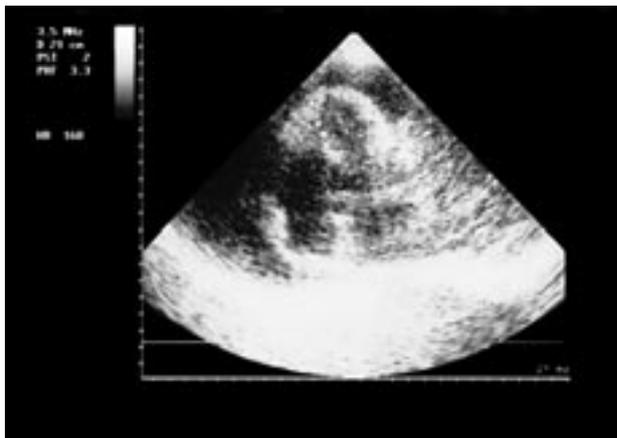


Figure 1. Large pericardial effusion in the apical four-chamber view (“swinging heart”).

with large pericardial effusion, which was not seen two days (Figure 3) and one month (Figure 4) after pericardiocentesis and the intrapericardial administration of cisplatin. In 20 of the 25 patients (80%) the pericardial effusion was haemorrhagic. No events of acute chest pain due to intracavity cisplatin infusion were observed. Transient atrial fibrillation was detected in three patients (12%) and was cardioverted by amiodarone (two patients) or electrically (one patient). Non-sustained ventricular tachycardia was observed in two patients.

The malignant aetiology of the pericardial fluid was confirmed by positive cytological examination in 24 of the 25 patients. In the remaining patient, who presented with signs of cardiac tamponade and negative cytology, pericardial effusion was attributed to late post-radiation pericarditis. The haematological profile was not affected by systemic cisplatin absorption in any patient (leucopenia, anaemia, thrombocytopenia).

Intrapericardial administration of cisplatin prevented recurrences of cardiac tamponade in 22 out of 24 patients, although small pericardial effusions (<0.5 cm) were detected in nine (37.5%) during the follow up period. Surgical intervention (left anterolateral thoracotomy and pleuropericardial window formation) was ultimately necessary in two cases: in the first patient because of the failure of cisplatin infusion to control pericardial fluid reaccumulation and in the second patient because of coexisting neoplastic cardiac encasement. In 4 out of 24 patients (16%), sclerotisation of the pericardial space was detected by echocardiography; however, there were no symptoms or signs of constrictive pericarditis. The median survival period was 4.5 months (range 3-92 weeks). Death was attributed to generalised

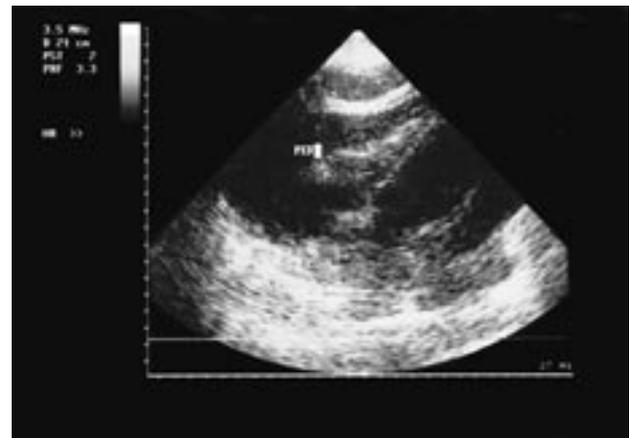


Figure 2. Large pericardial effusion in the subcostal four-chamber view in the same patient.

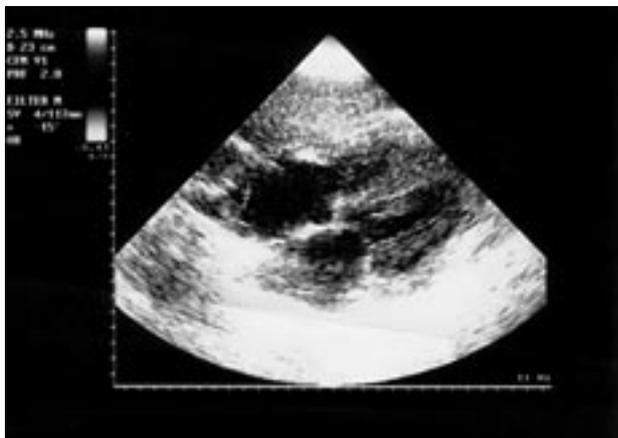


Figure 3. Absence of pericardial effusion seven days after pericardial drainage and intrapericardial cisplatin administration in the same patient (subcostal four-chamber view).

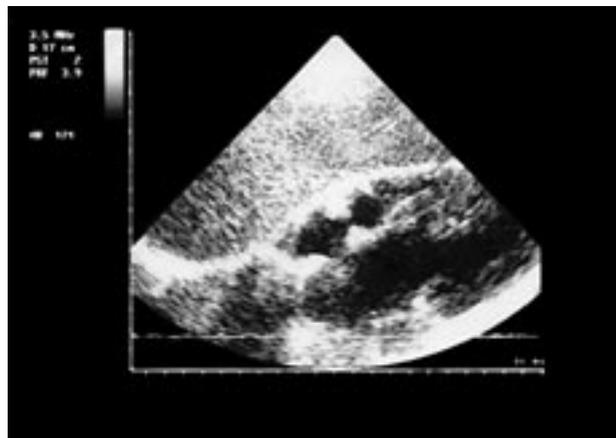


Figure 4. Absence of pericardial effusion one month later with increased "echogenicity" of pericardia in the same patient (subcostal four-chamber view).

carcinomatosis causing respiratory failure in all patients. No patient died of recurrent cardiac tamponade.

Discussion

The survival of patients with lung adenocarcinoma and malignant pericardial effusion depends mainly on the patient's condition, the presence of metastases, response to additional systemic treatment, local treatment and the prevention of recurrence of cardiac tamponade. Despite the obvious clinical significance of malignant pericardial effusion leading to cardiac tamponade, there are no prospective, randomised trials evaluating the effectiveness of the local infusion of various agents to control recurrence and improve mortality.

Intrapericardial infusion of cytotoxic or/and sclerosing substances

Data from the literature indicate that recurrence of pericardial effusion in various malignancies may be prevented by the intrapericardial instillation of thiotepa,^{18,19} bleomycin,²⁰⁻²² mitoxanthrone,²³ mitomycin C,²⁴ vinblastine,²⁵ interferon/interleukin-2²⁶ and OK-432.²⁷ In addition, tetracycline has been used as a pure sclerosing agent.²⁸⁻³² Colchicine has also been administered occasionally in patients with amyloidosis and chemoresistant multiple myeloma.³³

The intrapericardial instillation of thiotepa was extremely effective, preventing cardiac tamponade in patients with breast cancer in approximately 79-83%,^{18,19} but had limited efficacy in patients with lung cancer. Infusion of mitomycin C was successful in controlling

pericardial reaccumulation in 75-83% of cases.²⁴ The intrapericardial administration of tetracycline is often painful, requires multiple infusions and may cause late constrictive pericarditis.^{28,32}

Although the infusion of radioactive isotope ³²P-colloid³⁴ is very effective (94.5%) in controlling the recurrence of malignant pericardial effusion, its use is difficult in routine clinical practice.

Intrapericardial infusion of cisplatin

In a study by Tomkowski et al,¹¹ 8 out of 46 patients (17.4%) with malignant pericardial effusion died within 30 days after pericardiocentesis due to advanced malignancy. Cisplatin administration prevented reaccumulation of pericardial fluid in about 92% of the patients. In particular, the effectiveness of treatment in the subgroup of patients with non-small cell lung cancer who survived more than 30 days was 93.5% and the median survival period was 102.5 days. Transient atrial fibrillation was observed in 15.2% of patients and sclerotisation of the pericardial space confirmed by echocardiography was achieved in 10.9%, without symptoms and signs of constrictive pericarditis.

In a study by Maisch et al,¹² intrapericardial cisplatin instillation achieved a positive treatment effect in 92.8% of patients over a three-month period and 83.3% at six-months' follow up. Patients with lung cancer had fewer pericardial effusion recurrences (4.5%) compared with patients suffering from breast cancer (37.5%). Cardiac ischaemia related to cisplatin infusion was observed in one of 42 patients, without other severe complications.

Fiorentino et al³⁵ studied six patients treated with pericardiocentesis. Intracavity cisplatin (50 mg) was given during five consecutive days and repeated two to three weeks later in case of recurrence. Complete response was reported in 50% of patients.

Tordini et al³⁶ instilled 50 mg intracavity cisplatin in nine patients with symptomatic pericardial effusion (seven with lung cancer and two with breast cancer) after pericardial drainage and achieved prevention of recurrence in 88.9%. Lestuzzi et al³⁷ proposed intrapericardial chemotherapy according to the chemosensitivity of the primary tumour: 50 mg of cisplatin for lung cancer metastases and 30 mg of bleomycin for breast cancer metastases.

In our study all patients had lung adenocarcinoma and symptomatic malignant pericardial effusion. Intrapericardial cisplatin infusion prevented recurrence of cardiac tamponade in 91.5% of cases. Nowadays, pericardial infusion is considered severe, based on echocardiographic criteria, when the diastolic epicardial-pericardial separation exceeds 20 mm at both the posterior and anterior ventricular walls. However, in 28% of our patients discrete pericardial implantations or infiltrations were detected and in certain cases diffuse neoplastic deposits in the pericardium, with likely consequence a reduction in its compliance, meaning that a smaller quantity of fluid (mean 750 ml) could cause cardiac tamponade. Furthermore, the diagnosis of cardiac tamponade is based on clinical criteria and is related not only to the quantity but also to the rate of production of pericardial fluid. After complete pericardial drainage, the majority of patients not treated by intracavity chemotherapy develop haemodynamically significant pericardial effusion and eventually lethal cardiac tamponade.^{5,8,9} We observed atrial fibrillation and asymptomatic pericardial sac sclerosis at similar rates to those reported by other investigators.^{11,12}

An advantage of the treatment is that cisplatin infusion neither causes pain nor influences the haematological profile, because of the minimal systemic absorption from the pericardium. Intrapericardial fibrosis due to cisplatin infusion does not cause constrictive pericarditis even in long-term survivors. On the other hand, the exaggerated sclerosing process after intrapericardial instillation remains the main problem of other pure sclerosing agents.^{27,32}

It is well known that hilar lymphatic drainage participates in the early manifestation of malignant pericardial effusion during the course of lung cancer.³⁸ After intrapericardial cisplatin administration, high concentrations of this substance probably exist in do-

mestic lymphatic vessels, debulking the local neoplastic burden, improving drainage and consequently preventing recurrence of pericardial effusion.

Our study indicates that intracavity infusion of cisplatin in combination with systemic chemotherapy (paclitaxel-cisplatin), especially in patients with lung adenocarcinoma and metastatic pericardial effusion, improves prognosis and survival without any serious local or systemic adverse events.

Limitations of the study

The study lacked a control group, namely, patients who had no intracavity drug infusion following pericardial drainage. However, the large recurrence rate of malignant cardiac tamponade in the absence of such intracavity chemotherapy or sclerotherapy^{12,13} made such a design undesirable. Furthermore, cisplatin was not compared with other sclerosing agents. However, the number of cases of lung adenocarcinoma with malignant cardiac tamponade is relatively small (in five years only 25 such patients were referred to our hospital, which is the Oncology Centre of Northern Greece, covering 3.5 million residents), while this tumour shows a rather high chemosensitivity to the drug in question.

Conclusion

Intrapericardial cisplatin administration after pericardial drainage is an extremely effective and safe method of preventing the recurrence of haemodynamically significant pericardial effusion in patients with lung adenocarcinoma.

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