Objective: Pericardial involvement is a common feature in different neoplastic diseases, having a strong influence on the natural history of the disease and on the quality of life of the patients. This study was performed in order to investigate the long-term effects of intracavitary treatment with thiotepa in the reduction of pericardial effusion (PE) recurrences.

Design: Prospective controlled intervention study.

Setting: European Institute of Oncology, Milan, Italy.

Patients: We studied 33 patients, 15 men and 18 women, with malignant PE, who were affected by breast cancer (11 patients), lung cancer (16 patients), microcytoma (4 patients), endometrial cancer (1 patient), and melanoma (1 patient).

Intervention: All patients with large PE, with or without cardiac tamponade, underwent percutaneous pericardiocentesis (PC) under echocardiographic monitoring. Patients with neoplastic cells in drained fluid were considered to be eligible for treatment. After drainage, the catheter was maintained in the pericardial sac for the instillation of a sclerosing, alkylating antiblastic agent (thiotepa) on days 1, 3, and 5 after the PC (15 mg at each step).

Results: No procedure-related complications or side effects were observed. Two patients died because of disease progression, without PE evidence. No PE occurred in the remaining patients during the first month. Three recurrences occurred (9.1%), requiring additional PC and intrapericardial treatment. The median survival time was 115 days (range, 22 to 1,108 days) in the overall population, and 272 days in patients with breast cancer.

Conclusions: Intrapericardial treatment with thiotepa carries a minimal risk and is a repeatable procedure that can dramatically increase quality of life, or even can improve survival and the natural history of disease in cancer patients.

Key words: antineoplastic agents; cardiac tamponade; neoplasms; pericardial effusion; thiotepa

Abbreviations: NSCLC = non-small cell lung cancer; PC = pericardiocentesis; PE = pleural effusion

Pericardial diseases and pericardial involvement are an increasingly common complication of neoplastic diseases, which can be life-threatening not only in patients with unresponsive or aggressive terminal malignancies, but also in patients with otherwise favorable prognoses.

Early and successful therapy for patients with pericardial disease is therefore crucial in significantly increasing life expectancy, or in improving palliation.
and quality of life. Different methods may be used to treat malignant pericardial effusions (PEs), but the “gold standard” therapy in this subset of patients is yet to be defined. The present study was designed to assess the short-term safety and usefulness, as well as the long-term efficacy, of pericardiocentesis (PC) in association with intracavitary chemotherapy by means of an active antiblastic sclerosing agent, thiotepa, in patients with large malignant PEs.

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Study Population

Following the criteria reported above, 33 patients (15 men and 18 women) were considered to be eligible for the study. None of these patients had a history of cardiovascular disease. Breast cancer was the primary neoplasm in 11 patients, non-small cell lung cancer (NSCLC) was the primary neoplasm in 16 patients, and the remaining patients were affected with microcytoma (4 patients), melanoma (1 patient), and endometrial cancer (1 patient). All patients were receiving systemic chemotherapy at the time of the procedure, and at least one metastatic site other than pericardium was present. The study was approved by the local ethics committee, and informed consent was obtained from each patient. The protocol strictly adhered to the principles of the Declaration of Helsinki.

Study Protocol

PC was performed percutaneously under echocardiographic and ECG monitoring, according to a technique that has been described elsewhere. Correct catheter position was assessed by injecting boluses of isotonic saline solution and observing the echocontrast localization. After the initial drainage, the catheter was left in the pericardial space. The fluid from drained effusions was analyzed for cytopathologic features. On the following day (day 1), after further pericardial drainage, the intracavitary treatment was carried out. This consisted of a 15-mg bolus of thiotepa and 30 mg hydrocortisone. The procedure was monitored by ECG and echocardiography to assess both cardiac injury and complete pericardial drainage. On days 3 and 5, we performed further drainage of newly formed fluid, as well as the administration of the same drugs to a total amount of 45 mg thiotepa over 3 days. Twenty-four hours after administering the last dose, the catheter was removed. All patients underwent further clinical cardiologic examinations, ECG, and echocardiogram 30 days after the initial procedure, and every month thereafter. Information about the causes and times of deaths was obtained by the medical oncology outpatient service.

Statistical Analysis

The study was designed as a case series with a prospective analysis of all patients with known PE treated with PC and intracavitary thiotepa. The results are expressed as the mean ± SE, and the follow-up results are expressed as the median survival time. Survival data are plotted by the Kaplan-Meier curve.

Results

Clinical and Echocardiographic Data

Before undergoing PC, all patients showed poor performance status, complaining of weakness, dyspnea (New York Heart Association functional class III, 56%; New York Heart Association class IV, 44%), and chest pain/discomfort (28% of patients).

At the ECG, all patients showed sinus tachycardia, and 10 patients showed low voltages in precordial leads. Electrical alternance was present in two patients. No patient manifested cardiac rhythm disturbances.

Echocardiography: A large PE (ie, > 3 cm) was present in all patients, and 24 patients showed one or more echocardiographic criteria of cardiac tamponade (ie, right atrium and/or right ventricle diastolic collapse observed both in M-mode and 2-D mode, or the presence of transmitral Doppler pattern of flow reduction during inspiration). Intrapерicardial metastases were seen in four patients as hyperechogenic masses through pericardial layers.

Procedure

The mean amount of drained fluid during the initial PC was 749 ± 203 mL. The mean amount on day 1 was 243 ± 204 mL, the mean amount on day 3 was 78 ± 11 mL, and the mean amount on day 5 was 54 ± 11 mL. The pericardial fluid was hemorrhagic in all patients.

During the procedure, no general or cardiovascular complication was observed, as confirmed by clinical examination, radiograph, ECG (ie, no significant arrhythmic or ischemic events), and echocardiography (ie, no alterations in wall motion or valvular dynamics). After undergoing PC, all patients showed rapid and almost complete improvement of symptoms. On days 1, 3, and 5, during thiotepa instillation, no acute clinical or ECG alterations were observed, and no patients complained of chest pain or circulatory symptoms. No significant signs of myelosuppression were observed. All patients were
discharged from the hospital 24 h after the last intrapericardial instillation. The mean duration of hospital stay after undergoing PC was 6 ± 1 days.

Follow-up

Two patients died due to disease progression on the 22nd and 25th days after undergoing the procedure. No echocardiographic evidence of PE was detected in either patient. At the first evaluation (1 month after the initial procedure), recurrence was not observed in the remaining patients. Clinical examination revealed no heart failure-related symptoms, and the echocardiogram did not show any sign of significant PE. Recurrences occurred in three patients, at 224, 87, and 70 days after undergoing PC. Treatment with PC plus thiotepa was again performed with good early results and the absence of further effusions.

At the time of writing, three patients were still alive (breast cancer, two patients; NSCLC, one patient) 55, 87, and 101 days after undergoing PC, with no evidence of effusion recurrence. No patients died from PE recurrence. The median survival time for all patients was 115 days (range, 22 to 1,108 days). Those patients with breast cancer showed a median survival time of 272 days (range, 47 to 1,108 days), which is longer than that in patients with NSCLC (median survival time, 85 days; range, 22 to 170 days) [Fig 1].

Discussion

Malignant PE and cardiac tamponade are common complications in patients with neoplastic diseases. In autopsy series, the prevalence of pericardial involvement varies from 4% in general autopsies, to 15 to 30% in autopsies of cancer patients. In previously asymptomatic patients, peri-

Figure 1. Kaplan-Meier survival curves of studied patients. □, all patients; ●, patients with breast cancer; ○, patients with lung cancer.
cardiac tamponade was the immediate cause of death in about 85% of cases. Currently, the improved survival of cancer patients leads to the increased incidence of secondary patterns such as malignant PE. Neoplasms most frequently associated with pericardial involvement include breast cancer, lung cancer, lymphomas, leukemia, and melanoma.

The possible therapeutic options vary from systemic chemotherapy to PC, surgical pericardial evacuation, or mixed procedures. PC is an emergency life-saving procedure, but, regrettably, it is associated with a very high early incidence of PE recurrences (up to 40%). Better results can be obtained if local intrapericardial chemotherapy is performed. Different agents have been used, but most data relate to the use of tetracycline hydrochloride and its derivatives. Other compounds, such as bleomycin, cisplatin, nitrogen mustard, fluorouracil, teniposide, thiotepa, or even radionuclides, also have been studied. At present, only tetracyclines have shown significant positive effects, as they are capable of controlling about 80% of PEs in short-term follow-up. Suitable symptomatic procedures are subxyphoid pericardiectomy and the percutaneous balloon pericardial window, which are generally performed under local anesthesia. This procedure offers the immediate relief of tamponade and, apparently, the prevention of local recurrences in nearly 90% of the reported cases, with a low incidence of major complications.

In contrast to the described surgical procedures, which can be classified as mere “symptomatic” tools, PC associated with intracavitary therapy is more than a simple drainage technique. Acting as a chemotherapeutic and “etiologic” treatment, it is effective, not only in the voiding of the neoplastic effusion, but also in the inhibition of its further production. Moreover, although the implications of the possible intrathoracic dissemination of neoplastic fluids (generally induced by surgical procedures) are unknown, it is safer to perform a closed pericardial treatment as a first-choice intervention. In fact, our patients who were treated with intrapericardial thiotepa showed a long-term survival period that was unexpected in a subset of patients with an otherwise well-defined, very poor prognosis, due to both the advanced neoplastic growth and the severity of the PE. Although not supported by a randomized trial, our data enabled us to consider treatment with PC with local intracavitary pericardial chemotherapy as a first-choice procedure, followed by the opening of percutaneous windows only in cases of further multiple PE recurrences.

Past experience with intrapericardial therapy has focused mostly on the use of tetracycline derivatives, which show consistent short-term efficacy in preventing early recurrences, even in the presence of side effects (Table 1). It should be noted, however, that the effusion control of tetracyclines is due only to sclerosing activity and not to specific antineoplastic action. Thiotepa, on the contrary, is both an alkylating and sclerosing agent, and has been used for many years in the treatment of solid tumors and malignant effusions. Despite similar or even better results in recurrence prevention in comparison to that of tetracyclines, thiotepa instillation is not associated with significant local or systemic side effects. It is worth noting that none of the patients included in the study complained of chest pain, as is frequently reported during the instillation of tetracyclines. Moreover, our patients did not experience myelosuppression because we utilized a total thiotepa dose of < 60 mg in order to reduce the risk of myelotoxicity. Indeed, a higher risk of myelotoxicity has been described with doses of ≥ 60 mg, even if the drug is administered via the intracavitary

### Table 1—Different Approaches and Results in PE Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Malignant Cells</th>
<th>Patients, No.</th>
<th>30-d PE abs, %</th>
<th>Med Surv, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girardi et al</td>
<td>Sclerosis (thiotepa)</td>
<td>Y/N</td>
<td>37</td>
<td>92</td>
<td>NA</td>
</tr>
<tr>
<td>Girardi et al</td>
<td>Different</td>
<td>Y/N</td>
<td>72</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>Wall et al</td>
<td>P-P window</td>
<td>NS</td>
<td>57</td>
<td>87</td>
<td>59</td>
</tr>
<tr>
<td>Moores et al</td>
<td>Subxyphoid drainage</td>
<td>Y</td>
<td>42</td>
<td>NA</td>
<td>56</td>
</tr>
<tr>
<td>Okamoto et al</td>
<td>P-P window</td>
<td>NS</td>
<td>51</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Wilkes et al</td>
<td>PC</td>
<td>Y/N</td>
<td>26</td>
<td>53</td>
<td>NA</td>
</tr>
<tr>
<td>Shepherd et al</td>
<td>Sclerosis (tetracycline)</td>
<td>NS</td>
<td>54</td>
<td>81</td>
<td>NA</td>
</tr>
<tr>
<td>Davis et al</td>
<td>Sclerosis (tetracycline)</td>
<td>NS</td>
<td>33</td>
<td>91</td>
<td>NA</td>
</tr>
<tr>
<td>Liu et al</td>
<td>Sclerosis (dox-bleo)</td>
<td>Y/N</td>
<td>21</td>
<td>75</td>
<td>NA</td>
</tr>
<tr>
<td>Bishinotis et al</td>
<td>Sclerosis (thiotepa)</td>
<td>Y</td>
<td>19</td>
<td>NA</td>
<td>330</td>
</tr>
<tr>
<td>Current study</td>
<td>Sclerosis (thiotepa)</td>
<td>Y</td>
<td>33</td>
<td>100</td>
<td>115</td>
</tr>
</tbody>
</table>

*Malignant cells = evidence of neoplastic cells in drained fluid; 30-d PE abs = patients without PE recurrences in the first 30 days after treatment; Med Surv = median survival of treated patients; Y = yes; N = no; NS = not specified; NA = not available; P-P Window = pleuro-pericardial window opening; dox = doxycyclines; bleo = bleomycin.*
Furthermore, because of its very fast absorption by the pericardium, the total dosage of thiotepa was administered over 3 days.

A few studies already have been reported regarding thiotepa effectiveness in the treatment of malignant PEs. It is important to emphasize that the work of Bishiniotis et al., which showed better overall results, was conducted only in women with breast cancer, a particular population that, even in our study, was associated with a longer median survival, which is similar to the data of Bishiniotis et al.

The current study was admittedly biased by the lack of a control group. This is encountered in almost all series published in the literature (in the absence of standardized case-control trials), and is mostly due to the heterogeneity of oncologic patients. Although no evidence-based conclusions can be drawn from our study, we believe that the safe and satisfactory nature of the clinical results of the proposed therapeutic protocol is worth reporting. It is also important to note that we evaluated the follow-up results separated according to primary disease, showing a relatively greater benefit of sclerotherapy in patients with breast cancer.

We concluded that the aggressive treatment of malignant PEs, which is associated with local chemotherapy, results in a higher quality of life and a longer life expectancy with an absence of significant side effects. Accordingly, these PEs should not be considered as a terminal event, but as a treatable condition requiring a true therapeutic intervention instead of a mere palliative approach. It is our opinion that PC, associated with intracavitary thiotepa treatment, given its low cost, low risk, and safety, can seriously be considered as a first-choice procedure in approaching the treatment of patients with neoplastic PEs.

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