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Neoplastic pericardial disease: Old and current strategies for diagnosis and management

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Abstract

The prevalence of neoplastic pericardial diseases has changed over time and varies according to diagnostic methods. The diagnostic factor is usually the detection of neoplastic cells within the pericardial fluid or in specimens of pericardium, but the diagnosis may be difficult. Accurate sampling and cytopreparatory techniques, together with ancillary studies, including immunohistochemical tests and neoplastic marker dosage, are essential to obtain a reliable diagnosis. The goals of treatment may be simply to relieve symptoms (cardiac tamponade or dyspnea), to prevent recurrent effusion for a long-term symptomatic benefit, or to treat the local neoplastic disease with the aim of prolonging survival. Immediate relief of symptoms may be obtained with percutaneous drainage or with a surgical approach. For long term prevention of recurrences, various approaches have been proposed: extended drainage, pericardial window (surgical or percutaneous balloon pericardiostomy), sclerosing local therapy, local and/or systemic chemotherapy or radiation therapy (RT) (external or with intrapericardial radionuclides). The outcomes of various therapeutic approaches vary for different tumor types. Lymphoma and leukemias can be successfully treated with systemic chemotherapy; for solid tumors, percutaneous drainage and the use of systemic and/or local sclerosing and antineoplastic therapy seems to offer the best chance of success. The use of "pure" sclerosing agents has been replaced by agents with both sclerosing and antineoplastic activity (bleomycin or thiotepa), which seems to be quite effective in breast cancer, at least when associated with systemic chemotherapy. Local chemotherapy with platinum, mitoxantrone and other agents may lead to good local control of the disease, but the addition of systemic chemotherapy is probably relevant in order to prolong survival. The surgical approach (creation of a pericardial window, even with the mini-invasive method of balloon pericardiostomy) and RT may be useful in recurring effusions or in cases that are refractory to other therapeutic approaches.

Key words: Neoplastic pericarditis; Neoplastic pericardial disease; Diagnosis; Therapy

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INTRODUCTION

The reported prevalence of neoplastic pericardial diseases has changed over time and has varied according to diagnostic methods. In an autopsy series, it has been found in 2%-4% of the general population, in 7%-12% of cancer

patients and, among these, in 19%-40% of patients dying of lung cancer, 10%-28% dying of breast cancer and in 9%-28% with leukemia or lymphoma, apparently with a trend toward increasing frequency among lung cancer patients in more recent years and a decrease in haematologic malignancies. This trend can only be observed in the very long term, however. In a necropsy study between 1974 and 1987, the prevalence of primary tumors showed little variation over time[1-8]. Autopsy studies overestimate the clinical problem because they include mostly terminally ill patients and identify even microscopic metastases or small effusions without clinical relevance. In two studies comparing clinical and pathologic features of pericardial metastases, 60%-70% were clinically non significant[9,10]. In fact, in a study on 2700 breast cancer patients, seen from 1987 to 1997, symptomatic neoplastic pericardial effusion was only diagnosed in 19 (0.7%)[11]. This finding was confirmed by a retrospective study on 1600 patients with leukemia who had one or more echocardiographic examinations during their illness. A pericardial effusion was detected in 325 (20%) cases, but was very mild in 70% of the cases. It was moderate to large in < 9% of the cases and only 10 (3%) patients required pericardiocentesis (4 of them had leukemic blasts in the pericardial fluid). Approximately 75% of the patients with pericardial effusion had concomitant pleural effusion, and the presence of pericardial effusion did not have any impact on survival. In this study, the incidence of neoplastic effusion appeared to be treasurable[12]. Among lymphoma patients, a particular subgroup is the one with primary effusion lymphoma, which usually affects human immunodeficiency virus-infected patients, but has been described occasionally in immunocompetent patients, and is characterized by a clinical appearance of pleural, pericardial and/or peritoneal effusion without solid masses or lymph node involvement[13,14]. This particular type of lymphoma generally has a poorer prognosis compared to other non-Hodgkin's lymphomas (NHL). It has peculiar behaviour characteristics and can be treated, not only with chemotherapeutic agents, but also with antiretroviral therapy[15,16]. Among symptomatic effusion, on the other hand, cancer was the principal cause in the past, but its prevalence has decreased over time. In a retrospective analysis on 1127 pericardiocenteses performed at Mayo Clinic on 977 patients over 21 years, malignant effusion accounted for 50% of the procedures in years 1979 to 1986, 45% in years 1986 to 1993 and 25% between 1993 and 2000[17]. According to the authors, this change was due to an increase in other causes of pericardial effusion (mainly postoperative or perforation from invasive procedures) rather than to a decrease of malignant pericarditis cases, which actually increased from 91 to 159 from the first to the second period mentioned above. Nevertheless, in the third period (1993-2000) there were only 125 cases of neoplastic pericarditis. This inversion of the trend might be due both to an improvement in the treatment of cancer and to the increasing use of routine computed tomography (CT), magnetic resonance imaging, echocardiography and positron emission tomography that leads to an early detection and therapy of small effusions, which then prevents the need for pericardiocentesis. The decrease in neoplastic etiology among large pericardial effusions in the past years seems to be confirmed by a Spanish study and an Italian study covering the years 1998-2002 and 1996-2003, respectively, with results showing a prevalence of 13% and 7.3%, respectively[18,19]. Since the relative proportion of neoplastic pericarditis depends also on the prevalence of other causes of effusion, it may vary widely in particular populations. In a Turkish report, 15/50 patients (30%) had neoplastic pericarditis, but there were no cases of post-surgical pericardial effusion in this group. However, in a larger study from Turkey, there were only 46/368 cases of neoplastic pericarditis (13%) in a population with high prevalence of uraemic pericardits[20,21]. On the other hand, in a report from Brigham and Women's Hospital of Boston, 40% of the patients undergoing pericardiocentesis had malignant effusions (27.4% definite and 12.3% likely), with only 0.9% with infectious causes in the same cohort[22]. A South Korea study reported 61/116 (53%) of the cases as "malignant effusions", but this diagnosis was confirmed by cytology in only 27 cases (44% of the cancer subgroup, 27% of the entire cohort)[23]. Among neoplastic pericardial disease diagnosed *in vivo*, as in autopsy studies, lung and breast carcinoma are the more frequent primary tumors[24]. In lung cancer, the metastatic pathway to the pericardium is almost always lymphatic (usually from the dorsal side). This finding explains why pericardial effusion is often large, and why neoplastic cells may be found in the pericardial fluid even if absent in pericardial biopsies[25,26].

DIAGNOSIS

As mentioned above, pericardial effusion in patients is not always due to malignancy; other causes of pericardial effusion are radiotherapy, lymphatic drainage impairment and hypoalbuminemia. The diagnostic clue is usually the detection of neoplastic cells within the pericardial fluid or in specimens of pericardium. But the diagnosis is not always simple, and sometimes impossible. Reactive lymphocytes may be morphologically indistinguishable from malignant cells in NHL. On the other hand, in Hodgkin's disease, effusion cytology is often non diagnostic. Accurate sampling and cytopreparatory techniques, together with ancillary studies (immunocytochemistry, flow cytometry, morphometry and cytogenetics) may help in the diagnosis, which usually requires a definition of the lymphoma subtype as well[27]. In solid tumors, on the other hand, effusion cytology may be extremely difficult because mesothelial cells exhibit a spectrum of cytomorphologic features, sometimes mimicking carcinoma[28,29]. In the case of mesothelioma, the cytologic diagnosis is even more difficult because hyperplastic or reactive mesothelial cells may mimic malignant mesothelioma. Differentiation from metastatic adenocarcinoma may be challenging and, on the other hand, effusion may have no cytologic evidence;

the sensitivity has been reported to be 38%-50%[30,31]. Some problems may arise in cytological evaluation due to the storage of effusion fluid. When the amount of neoplastic cells is relatively low, the probability to detect them is obviously higher when examining the entire drained fluid rather than a few milliliters[32]. Moreover, benign cells may degenerate during storage and, for this reason, effusion specimens should be received in the cytopathology laboratory immediately after drainage in the fresh state or refrigerated, and should be stored at 2-8℃ (best at 4℃)[33,34]. A number of immunohistochemical markers have been selected to improve the sensitivity and specificity of the diagnosis; for optimal use, cell block preparations, in addition to smears, are required[35-39].

In cytology-negative samples, or whenever the diagnosis is equivocal, the dosage of tumor markers, such as carcinoembryonic antigen (CEA), serum cytocheratin 19 fragments (CYFRA 21-1), neuron-specific enolase (NSE) and carbohydrate antigens CA 125, CA 15-3 and CA 19-9, in the effusion may be helpful in the setting of solid tumors[40-44]. These markers must be used cautiously because the cut-off values have not been well defined. Different tumors may be identified by different markers and the sensitivity of every marker could be rather low. Nevertheless, specificity is high for some markers and tumors (among carcinomas: 80%-100% for CEA, 80%-97% for NSE and 70%-100% for CYFRA), and the combination of two or more tumour markers leads to a higher diagnostic value[45]. Paganuzzi found that a high value of CYFRA 21-1 with low CEA in the pleural fluid can identify patients with mesothelioma, while Dejmek used a combination of CEA, epithelial membrane antigen, BerEp4 and hyaluronan in this setting, with a sensitivity of 79% and a specificity of 100%[44,46]. A meta-analysis of published data showed good performance with both CEA and CYFRA 21-1 in the differential diagnosis of pleural effusions. The majority of these studies was focused on pleural effusions (which are much more common and easily drained) but similar results have been obtained in pericardial effusions[47,48]. More recently, Her-2/neu has been added to the panel of possible markers in lung carcinoma effusions, but CEA is still the most accurate single diagnostic marker, followed by CYFRA 21-1, and the combination of a CEA > 6 ng/mL and CYFRA 21-1 > 60 ng/mL resulted in a sensitivity of 97.6% and a specificity of 91.4% in the most recent report[49]. After drainage of the pericardial fluid, samples of fluid are sent both to microbiology and pathology laboratories for culture, chemical tests and neoplastic marker dosages. The remaining fluid should be sent immediately to the pathology laboratory for centrifugation and cytological diagnosis, or refrigerated at 4℃.

Pericardioscopy has been suggested to further define the etiology of pericardial effusions, in general allowing mirate biopsies, and has been reported to significantly raise the probability of obtaining a diagnosis, compared to effusion cytology and fluoroscopy-guided biopsy, in the neoplastic setting[50-54]. In the diagnostic algorithm suggested by the European Society of Cardiology, pericardioscopy has been included among the optional procedures if other tests (ECG, blood analysis and effusion fluid analysis) are inconclusive (indication class Ⅱa)[55].

TREATMENT

The goals of treatment may be simply to relieve symptoms (cardiac tamponade or dyspnea), to prevent recurrent effusion for a long-term symptomatic benefit, or to treat the local neoplastic disease with the aim of prolonging survival. Immediate relief of symptoms may be obtained with percutaneous drainage or with a surgical approach. For the long term prevention of recurrences, various approaches have been proposed: extended drainage, pericardial window (surgical or percutaneous balloon pericardiostomy), sclerosing local therapy, local and/or systemic chemotherapy, radiation therapy (RT) (external or with intrapericardial radionuclides). It is hard to compare the efficacy of these methods on the basis of the many reports on the topic, because the diagnosis is often not well defined (large pericardial effusion in a patient with cancer classified as "malignant" even without cytology or neoplastic marker confirmation, as discussed above). The efficacy criteria, which are necessarily arbitrary, change in different reports and few prospective randomized studies have been published. Moreover, most of the older reports consider an intervention successful if the patient survived for 30 d without recurrence of symptoms or tamponade[56,57]. This approach has two main defects: first, the fixed time of observation (a patient dying for non-cardiac causes without pericardial disease would be considered as "unsuccessfully treated", while one with relapsing tamponade after 32 d would be considered successfully treated); and second, cardiac tamponade depends not only on the entity of pericardial effusion but also on many variables, such as blood volume, right and left ventricular wall thickness and rate of accumulation of pericardial fluid. Moreover, one of the main signs (pulsus paradoxus) may be absent with atrial septal defect, left ventricular dysfunction or regional tamponade[58-60]. These limitations (particularly in cancer patients that can have a variety of concomitant problems, such as pleural effusion, intrathoracic masses, anaemia, low blood proteins, which can mimic signs and/or symptoms of cardiac tamponade or heart failure) have been thoughtfully addressed by Vaitkus *et al*[61] in a 1994 review in which several treatment approaches were compared. In this review, the authors considered an intervention "successful" if the patient survived the procedure, the symptoms did not recur, and no other interventions directed at the pericardium were required, regardless of the length of survival". This definition still has two limitations: first, there are the above mentioned problems in assessing symptoms, and second, the decision to undertake subsequent interventions may depend on the attitudes of both the physician and patient. The outcome would be better evaluated with objective outcomes, such as a complete response, partial response, stable disease and progression, as usual with solid tumors.

However, effusions are considered "not measurable" in oncologic staging[62]. Nevertheless, a semiquantitative assessment of pericardial effusion is possible by measuring the daily drained fluid from the catheter or by echocardiography, as done usually in the more recent reports[63,64].

Percutaneous drainage

In large pericardial effusions, percutaneous drainage using the Seldinger technique is useful to prevent or rapidly relieve symptoms of tamponade. Echocardiographic guidance reduces the risk of cardiac puncture or other complications, and is the presently accepted routine method[65]. Without any additional treatment, the rate of recurrence is high (up to 40%) and by extending the drainage for several days, the rate of recurrence is reduced[66]. Systemic CT without further local interventions has been reported to be effective in lymphomas and in some cases of solid tumors (mostly breast and ovarian)[67-72].

Surgical treatment

The most commonly used surgical approach is pericardiotomy or the creation of a pericardial window connected to a drainage tube or draining into the pleural or peritoneal space (using the subxiphoid approach, a left thoracotomy or a ballon catheter). The efficacy of this approach may be due, not only to the creation of a persistent communication through which fluid is drained, but to the inflammatory process that promotes adhesion between parietal and visceral pericardium, as confirmed by a small autopsy study[73]. In a prospective study from Duke University, surgical subxiphoid pericardiotomy was done under local anesthesia in 77% of 57 patients with various diseases, with general anesthesia required in the others. Effusion recurred in 8 patients in 2 mo and in 9 (16%) in the first year. In the subgroup of neoplastic pericardial effusion (n = 13), the mortality was 54% at 2 mo and 92% at 12 mo follow-up[74]. In a report of 67 patients (26 with cancer, 14 with neoplastic pericardial involvement) treated with subxiphoid pericardial drainage, the overall success rate was 82%, but the median survival was 393 d in cancer patients with negative cytology *vs* 122 d for those with malignant pericardial involvement. No data on concomitant antineoplastic therapies were reported[75]. In a larger study by Becit *et al*[21], 368 patients had subxiphoid surgical pericardiostomy connected to an external drainage tube. General anesthesia was used in 6% (mostly children), while local anesthesia with sedation (ketamine) was used in 94%. Within 1 mo, 37 patients (most with tuberculous and uremic pericarditis) had relapsing pericardial effusion and had a pleuropericardial window made, without any recurrence thereafter. Eleven patients (3%), all in the bacterial pericarditis group, developed constrictive pericarditis requiring pericardiectomy. In a retrospective study, the risks and efficacy of subxiphoid pericardiostomy *vs* percutaneous pericardial drainage was compared in 117 patients[76]. The authors reported a significantly higher mortality (1/23, 4% *vs* 0/94) and complication rate (4/23, 17% *vs* 1/94, 1.1%) in the pericardial drainage group. It should be noted, however, that pericardiostomy was the first choice method of treatment, and percutaneous drainage was limited to patients "considered too hemodynamically unstable to undergo surgical subxiphoid pericardiostomy, even under local anesthesia". The patients with underlying malignancy were 64/117, and this subgroup had a median survival of 2.2 mo and a 1-year actual survival rate of only 13.8%, regardless of drainage technique. On the other hand, a more recent retrospective analysis of 60 neoplastic pericardial effusions treated either with percutaneous (n = 10) or surgical pericardiostomy (n = 50) did not report any death and did not observed any difference in time to recurrence in either group. The median overall survival was 6.1 mo, and was higher (7.9 mo) in patients with adenocarcinoma than in other cytologic types (1.25 mo, P < 0.01). Gross, describing the outcome of 43 solid cancer patients treated with different surgical approaches (21 subxiphoid pericardial window, 14 pleuropericardial window and 8 pericardiodesis with thiotepa), reported 2.1% mortality (myocardial rupture during finger exploration of the pericardial space), and 6.4% morbidity. Most of the patients had concomitant chemo- or RT and the median overall survival was 5.2 mo in patients with breast cancer and 3.2 mo in the others[77]. In the early 1990s, the use of percutaneous balloon pericardiotomy was suggested as an alternative, less invasive intervention. The method appeared to be safe, with short-term success in preventing tamponade, but the long-term outcome was poor in the large subgroup of neoplastic patients, with a mean survival of 3.3 mo[78]. In the following years, the technique was modified with the use of an Inoue balloon catheter and a double-balloon. The inflation of two adjacent balloons might have some advantages over a single large balloon: stronger tension and more secure location in the pericardial space. In a retrospective analysis of 50 patients with cancer, Wang reported a 90% success rate (prevention of recurring effusion) using this method, but a median survival rate of 4 mo overall, with a significantly shorter survival in the cytology positive subgroup[79]. Complications were fever (30%) and pneumothorax (20%). More recently, the outcome of 43 patients, with various cancers, treated with primary single balloon pericardiostomy has been reported[80]. In this report, pain was a common side effect and required opioids before and during the procedure; 7.4% of patients had reaccumulation of fluid requiring reintervention, and the median survival was only 56 d. The authors suggested this technique as the management of choice for malignant pericardial effusion, but an editorial comment suggested to consider this approach as a second choice after percutaneous catheter pericardial drainage[81].

Sclerosing therapy

The rationale for pericardial sclerosis is to mechanically prevent the reaccumulation of effusion after drainage, promoting adhesion of the visceral and parietal pericardial layers.

"Pure" sclerosing agents: The first agents used for this purpose were antibiotics, such as powdered tetracycline and doxycycline, according to previous favourable experience in pleural effusions. The rationale was to induce irritation, inflammation and subsequent fibrosis, but the exact mechanism of action of these agents is not yet clear. In fact, other irritating agents (such as sodium hydroxide) do not cause pericardial symphysis[82-85]. Actually, a cytostatic activity has been suggested as contributing to the therapeutic effect of tetracycline[86]. The main adverse effects of these agents were pain (reported in 20% of patients in spite of the addition of intrapericardial lidocaine, with occasional severe pain), fever (7%) and paroxysmal atrial fibrillation (8%). Minocycline, a tetracycline derivate, has also been suggested for pericardial sclerosis, but it caused severe pain in the majority of patients (sometimes requiring opiates to be controlled), and the sclerosing effect was found to be independent from the acute irritative effect of the drug[87,88]. The largest study on tetracycline or doxycycline sclerosis reported an outcome of 93 cancer patients (69 with positive and 21 negative cytology, 3 not determined), of whom 85 received sclerosis. The procedure was complicated by pain in 17 (20%), fever in 7 (8%), atrial fibrillation or flutter in 6 (7%) and was effective in 75 (81%). However, 50 patients required > 2 instillations and the median dose used was 1500 mg[84].

Cytotoxic sclerosing agents: Bleomycin (BLM), an anticancer agent with sclerosing properties used in pleural and peritoneal effusion for chemical pleurodesis, has been tested also in pericardial effusions. In one of the first reports, 5 patients (all also receiving systemic CT) had 30-60 mg of BLM intrapericardially, resulting in complete control of effusion in all cases. In 2 cases, an autoptic study was available and residual pericardial tumor implants were still present[89]. In one report, 5/5 patients treated by intrapericardial BLM had a survival rate of 1-29 mo without effusion recurrence (but no mention was made of post-mortem histopathology), and in another study, 5/7 had stable control of effusion[90,91]. In a randomized prospective study on 20 patients, BLM was as effective as doxycycline as a sclerosing agent (82% *vs* 67% without recurring effusion), but with much less morbidity (no pain in the BLM group *vs* 7/10 patients with pain requiring narcotic analgesics in the doxycycline group)[92]. In a prospective randomized study, the outcomes of 79 lung cancer patients with pericardial effusion (58 with positive cytology) treated either with intrapericardial BLM or pericardial drainage alone were compared[93]. There were 9 early deaths within 30 d (5 in the drainage arm and 4 in the BLM arm), 1 case of constrictive pericarditis and 1 of cardiac dysfunction, both in the BLM group. The median effusion failure-free survival was 30 d in the drainage alone arm and 57 d in the BLM arm ($P = 0.03$ by log-rank test), but in the subgroup analysis this advantage was more evident in the cytology negative patients. Moreover, the patients with surgical drainage had a longer effusion failure-free survival compared to those undergoing drainage with a Seldinger technique. Another confounding aspect was that 24 patients received systemic CT. The actual efficacy of sclerosing therapy was not fully evaluable in this heterogeneous group of patients. The immunomodulator OK-432 (a penicillin-treated powder) used in Japan for pleurodesis has also be tested in the pericardium, but it had several, frequent side-effects: fever, pain and rapid reactive reaccumulation of fluid[94,95]. Cytokines (interferon α, β, interleukin-2) have been used in various effusions (mostly pleural) with few side effects but the reported response rate ranged from 10% to 70% in different studies[96-98]. The intrapericardial use of these agents was limited, and is presently not commonly used. Triethylenethiophosphoramide (thiotepa) is another anticancer agent with sclerosing properties used for local therapy with good results and few side effects. A retrospective study on 60 patients (30 only with positive cytology) were treated either with intrapericardial sclerosis with thiotepa or surgery (pericardial window or partial pericardiectomy). This study showed no advantage of this procedure over another in preventing effusion recurrence, but pericardiocentesis was more cost-effective[99]. In this study, the morbidity and recurrence was higher using a surgical approach rather than pericardiocentesis. The overall median survival was 97 d, however, considering different tumors, patients with breast cancer had a median survival of 407 d and those with lymphoma or leukemia had a median survival of 138 d. On the other hand, there was no difference in survival with respect to the type of drainage procedure performed; no subgroup analysis was associated with systemic CT. In a study by Bishiniotis *et al*[64] on 19 women with breast cancer and cytology positive pericardial effusion treated with intrapericardial thiotepa (9 with systemic CT in addition), 15 had complete control of effusion at 6 mo follow-up and 4 had only mild (< 0.5 cm) recurrent or residual pericardial effusion. The median survival in these patients was 330 d. Thiotepa was used by Martinoni *et al*[100] in 33 patients (16 breast cancer, 15 lung cancer, 4 different tumors) with cytology positive effusions, without recurrence in 30 patients at a follow-up of 22 to 1108 d (median 115 d). All patients also received systemic CT, and the overall survival was longer in the breast cancer subgroup compared to the lung cancer group (median 272 d *vs* 85 d). The better outcome of breast cancer compared to other solid tumors has been reported by other authors[101].

Local chemotherapy

The rationale of local chemotherapy is to obtain a higher local concentration of the antineoplastic drug. There have been very few pharmacokinetic studies performed on intrapericardial chemotherapy, but all confirm this hypothesis. Intrapericardial instillation of teniposide (VM 26) in 3 patients resulted in very high concentrations of the intrapericardial drug (peak > 190 μg/mL) lasting up to 3 d (area under the curve of > 2600 μg/mL per hour), with very low plasma concentrations (< 1.7 μg/mL), while with intravenous infusion, the peak intrapericardial concentration was only < 5 μg/mL[102]. 5-fluorouracil had similar phar-

macokinetics[103]. The pharmacokinetics of carboplatinum (300 mg given intrapericardially and removed after 40 min) were studied by Moriya *et al*[63] in 7/10 patients with lung adenocarcinoma, obtaining similar results. In this study, there was one non responder and one recurrence after 89 d, which responded to repeated local carboplatinum. The survival was 29 to 176 d (median 69 d). The pharmacokinetics studies using various intrapleural or intraperitoneal chemotherapic drugs (doxorubicin, docetaxel, liposomal paclitaxel) always showed much higher local concentrations of the drug, compared to plasma concentrations, and a much longer persistence of the drug in the cavity, while the reabsorbed drug was quickly cleared from plasma[104-106]. The use of intrapericardial cis-platinum (DDP) was first reported in 1985 in a single case treated with 10 mg over 5 continuous days[107]. The same schedule was used by others in a small series of mostly lung cancer patients, obtaining good results[108-110]. In a study on 9 patients with various tumors, Tomkowski *et al*[111] had 2 long-lasting responses in lung adenocarcinoma also treated with systemic CT, but most of the patients died of cancer within 3 mo, and in all of the 7 patients who had an autopsy, neoplastic pericardial involvement was found even without pericardial effusion. Maisch *et al*[112] used 30 mg/sm of DDP in a single administration (removing the drug after 24 h) in 42 patients with various tumors also undergoing systemic CT, and observed a relapse in 3/8 (37.5%) breast cancer cases, 1/22 lung cancer cases, 1/2 Hodgkin's cases and in the only mesothelioma patient; the mean survival was 2.8 ± 1.3 mo. Bischiniotis *et al*[113] used 10 mg of DDP over 3 continuous days in 25 cases of lung adenocarcinoma, obtaining complete disappearance of effusion in 13 cases and residual small (< 0.5 cm) effusion in 9 cases; a surgical approach was necessary in 1 case of DDP failure and in 1 case of tumor encasement of the heart. In a recent study, 7 patients with esophageal cancer were treated with local DDP (10 mg 2-5 times), obtaining complete remission in all cases. The 4 patients who received local CT only survived 61-104 d, while those who were treated with systemic CT as well survived 126-268 d[114]. Other chemotherapeutic agents have been used intrapericardially; e.g. nitrogen mustard, mitomycin C, mitoxantrone, 5-fluorouracil, but only case reports or small series have been published, making it impossible to judge the response rates[57,115-117]. Musch *et al*[118] in 2003, reported 12 complete remissions and 3 partial remissions (small pericardial effusion) among 16 patients (8 bronchial, 7 breast, 1 stomach carcinoma) treated with 10-20 mg of mitoxantrone left in the pericardium for 24 h; the follow-up lasted 28-730 d (mean 6 mo). In a multicenter series of various tumors, the mean effusion-free period of the patients treated with local chemotherapy (various agents) was 372 d (median 223 d); at 1, 2, 6 and 12 mo, 58%, 52%, 33% and 16%, respectively, were completely effusion-free. In the subgroup of 88 lung cancer patients, the mean effusion-free period was 271 d (median 215 d) and the percentages for completely effusion-free at 1, 2, 6 and 12 mo were 65%, 57%, 35% and 18%, respectively[119].

Radiotherapy

External beam radiotherapy has been used for radiosensitive tumors, such as lymphomas, acute and chronic leukemias and breast cancer[120]. The intrapericardial instillation of radioactive agents, such as ^{32}P colloid, has been used with a success rate of > 90%; a single dose of 5 mCi ^{32}P colloid would result in a total irradiation dose of > 100 Gy[121,122]. The mechanism is probably a combination of cytotoxic effect and post-inflammatory adhesion. Although this therapy is apparently well tolerated, it has not become very popular, probably due to concern about radiation risk and the availability and cost of the radioactive colloid.

Combined surgical and medical approach

In a series of 51 cases of cardiac tamponade caused by lung cancer (90% with positive or suggestive cytology) treated with subxiphoid pericardial window, 31 did not receive any local treatment, 20 had intrapericardial injections of one or more of doses of mitomycin C, tetracycline hydrochloride or doxorubicin[123]. There was no significant difference in either therapeutic response (82% and 90%, respectively) or patient survival rates between the two treatment sub groups; 41 (80%) and 25 (49%) also received systemic CT or RT. Of 28 patients on whom autopsies were done, extensive neoplastic involvement of the heart was found in 6 (21%), diffuse fibrofibrinous adhesion between the epicardium and pericardium in 18 (64%) and partial adhesion with recurrent pericardial effusion in 4 (15%).

DISCUSSION

The epidemiology, possible therapies and prognosis of neoplastic pericardial diseases have changed over time. Currently, symptomatic pericardial effusions are more frequently due to lung cancer, hematologic malignancies and, in some communities, to mesothelioma, while breast cancer is less represented compared to the past. The prognosis of breast cancer pericarditis is better than that of lung cancer. Very few prospective randomized studies have been performed on different therapies, and the comparison of many observational studies is difficult since, in the largest studies, different tumors and/or different treatments were analyzed together. The most important bias in the articles reporting the efficacy of various local treatments is the fact that many or all patients also received systemic CT, making it difficult to discriminate the relative efficacies of the interventions. There is only one study that separately analyzed the patients treated with pericardial sclerosis, local, systemic and combined CT in a group of 137 patients (61 lung cancer). Simple drainage or sclerotherapy had significantly lower success rates compared to any CT. Among solid tumors, both local and combined (systemic and local) CT showed a statistically significant advantage compared to systemic CT alone, while in the lymphoma patients, the outcomes were similar regardless of the method of administration of CT[124]. This finding might be explained in two ways: first, lym-

phomas are usually very chemosensitive, and even lower drug concentrations may be effective; and second, as lung and other intrathoracic tumors metastasize to the heart mostly through the lymphatics, and lymphomas often through the hematogenous route, the effect of a drug administered or reabsorbed through the same way is stronger. In fact, the use of translymphatic CT in lung cancer has been recently proposed[125]. In a study comparing the four main strategies, there was little difference between local CT and local plus systemic CT regarding the rate of effusion control. However, the patients receiving a combined treatment survived longer. The rationale for local CT actually is to obtain local control of the disease, but the addition of systemic CT, acting on other possible metastatic sites, may favorably influence survival. Regarding drugs to be employed locally, it seems reasonable to use the most active drug for each single tumor. Mitoxantrone is effective in breast carcinoma and lymphomas, BLM is currently used in systemic CT of head/neck carcinomas, squamous cell carcinoma, Kaposi sarcoma and both Hodgkin's disease and NHL. Thiotepa is active in breast, bladder, ovarian carcinomas and in Hodgkin's disease. Platinum is indicated in testis, ovarian, bladder, lung (both small cell and non-small cell), gastric carcinomas, in mesothelioma and in NHL. Taxanes are also active in breast and lung carcinoma and have been proven to be effective in animals, but their use for neoplastic pericardial disease in the clinical setting has not yet been reported[126,127].

CONCLUSION

The incidence of neoplastic pericardial disease, in general, and its prevalence among different primary tumors, have shown little change over time and may differ widely among different populations. Overall, it is more frequent in lung cancer patients. The diagnosis may be challenging in some particular patients, but with the use of multiple diagnostic methods (cytology, immunohistochemistry and dosage of neoplastic markers in the pericardial fluid), it may be defined in almost all cases.

Therapy should be limited to the control of symptoms in terminally ill patients only. In all patients that have a chance of surviving at least a few months, the goals should be to obtain a complete and stable control of effusion as long as possible, and to try to improve survival as well. The first goal may be obtained both with sclerosing agents and with local CT. Among the sclerosing agents, BLM and thiotepa (both with cytotoxic effects as well) have been successfully used with fewer side effects compared to tetracyclines and seem to be mostly indicated for breast carcinoma. Among the "pure" chemotherapeutic agents, platinum and mitoxantrone are the most tested and, according to their use in systemic CT, platinum is suggested for lung and ovarian carcinomas and for mesothelioma, and mitoxantrone is suggested for breast and other carcinomas. The second goal (improving survival) may be obtained by systemic chemotherapy, possibly associated with local CT.

In pericardial effusion due to lymphoma, pericardiocentesis may be limited to hemodynamically impaired patients, since systemic chemotherapy may be very effective. Among solid tumors, the most chemosensitive (such as breast and ovarian carcinoma) may also be treated with systemic CT first. Should pericardiocentesis be performed (for worsening effusion or impending cardiac tamponade), local therapy with thiotepa, mitoxantrone, mitomycin C (or other drugs known to be effective for a given cancer in general, or in a particular patient) may be useful. Lung carcinoma is best treated with combined systemic CT and intrapericardial platinum. The most tested was cis-Platinum; different treatment schedules have been used for local instillation (10-20 mg in 20 mL over 3-5 continuous days, 50 mg/50 mL in single bolus) without any evident advantage of one over others. Radiotherapy, balloon pericardiostomy or surgical creation of a pericardial window may be considered in selected cases, such as relapsing tamponade, tumor encasement of the heart or pericardial constriction. With a thoughtful diagnostic and therapeutic approach, many patients with neoplastic pericardial disease may survive without recurrence for several months or even years.

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