Systemic chemotherapy in combination with pericardial window has better outcomes in malignant pericardial effusions

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Objective: Our aim was to compare systemic chemotherapy (CT) with drainage and with pericardial window in the treatment of neoplastic pericarditis in patients with various malignancies included in the International Neoplastic Pericarditis Treatment study.

Methods: Patients treated with systemic CT alone (Group A), CT plus drainage (Group B), or CT plus pericardial window (Group C) were included. Treatment response was defined as complete response (ie, no more pericardial effusion or masses), partial response (ie, reduced total score, without requiring further treatments), stable disease (ie, unchanged total score), or progressive disease (ie, increased total score). Patients with partial or complete response were considered responders.

Results: This preliminary report included 175 patients (56.6% male) with a mean age of 54.21 ± 14.26 years. Gender distribution, age, and follow-up duration was similar for all groups ($P > .05$). Prevalent cancer types were lung cancer (50.9%), breast cancer (14.9%), and lymphoma/leukemia (14.9%). Overall, 22.3%, 42.9%, and 34.9% of patients were in treatment group A, B, and C, respectively. There were 132 responders (75.3%). The rate of responders significantly differed between groups ($P < .001$); it was significantly higher in Group B than in Group A ($P < .05$) and in Group C than in Group B ($P = .006$). The significant factors affecting response were therapy ($P = .002$) and extent of effusion ($P = .037$). Kaplan-Meier analysis showed that patients in Group C had a significantly better survival rate than patients in the other groups ($P = .001$).

Conclusions: Systemic CT plus pericardial window is a more effective treatment option compared with systemic CT alone and systemic CT plus drainage in patients with malignant effusions. (J Thorac Cardiovasc Surg 2014;148:2288-93)

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See related commentary on pages 2294-5.

Pericardial effusion is a common problem causing morbidity and mortality in patients with malignancy. The prevalence of cardiac involvement in malignancies is between 5% and 20% in autopsy series and clinical studies.[1-4] The most common malignancies with pericardial effusions are lung carcinoma, lymphoma, leukemia, and breast cancer.[2,5,6]

There are several reasons causing pericardial effusions in malignancies. About 30% of cases are due to radiation therapy; mediastinal lymph node engorgement; systemic tumor treatment; and viral, bacterial, and autoimmune causes. In 70% of cases the effusion is due to neoplastic invasion of the pericardium, and systemic chemotherapy (CT) as the only treatment, often fails. The presence of a large effusion may require drainage of the fluid to avoid cardiac tamponade, but the effusion tends to relapse if additional treatments are not given. Drainage may be obtained through pericardiocentesis performed by inserting a catheter with the Seldinger technique, or creating a pleuropericardial window. Pericardial window creation is the most common surgical treatment used for neoplastic pericardial effusions in association to systemic CT, but there are a limited number of studies comparing its efficacy to simple pericardiocentesis. The international multicenter retrospective study called International Neoplastic Pericarditis Treatment (INPUT) study was planned to be conducted to evaluate the outcome of a large number of patients with neoplastic pericarditis treated according to the usual care in each institution (systemic CT, local CT, pericardial drainage, and pericardial window). In a preliminary report, the efficacy of 4 treatments alone or in combination (pericardial drainage, sclerosing therapy, or local or systemic CT) in a subgroup of lung cancer patients was analyzed.[7] In this

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Abbreviations and Acronyms
CT = chemotherapy
INPUT = International Neoplastic Pericarditis Treatment study
VATS = video-assisted thoracoscopic surgery

report, only lung cancer patients were included, and none of the patients had been treated by pericardial window, thus leaving the open question if pericardial window is more effective than drainage in preventing recurrences.

The aim our study was to compare the outcome of neoplastic pericarditis treated either with systemic CT alone (without drainage), with drainage, and with pericardial window formation in patients with various malignancies, among those included in the INPUT study.

MATERIALS AND METHODS

According to the INPUT study, the neoplastic nature of the effusion has to be confirmed by cytology, histopathology, or elevated tumor markers in patients undergoing drainage. Patients with small pericardial effusion did not undergo pericardial drainage; in those patients, the diagnosis of neoplastic effusion was confirmed by the presence of intrapericardial neoplastic masses (detected by computed tomography or positron emission tomography) or by cytology if the effusion worsened and was finally drained. Patients who died within 15 days (for causes not related to the pericardial procedures) or could not be followed-up were excluded. The ongoing INPUT study is currently including 11 centers from 5 countries. For our study, among the total group of 326 patients we considered the subgroup comprising 175 patients treated by systemic CT alone, without drainage (Group A); CT plus drainage (Group B); or CT plus pericardial window (Group C). We excluded 33 patients who did not receive any CT, and 118 patients who were treated by local CT alone or in combination with systemic CT. This subgroup included the patients observed in 8 centers in 3 countries, namely, Belgium, Turkey, and Italy. All patients received systemic CT according to their primary tumor and to the state of art at the time of their disease. The choice between catheter drainage and pericardial window depended on the routine approach in different hospitals.

Each patient was treated according to the clinical knowledge at the time of the treatment, to the attitude of cardiologists, oncologists, and surgeons of each hospital. Thus, neither ethic committee approval (no changes from routine local practice), nor informed consent was required (excluding the usual consent for invasive procedures).

The names of patients were obtained from hospital records, and follow-up data were obtained by follow-up appointments and from hospital records. The follow-up was based on imaging techniques (ie, echocardiography, computed tomography scan, magnetic resonance imaging, and positron emission tomography) or autopsy data. Telephone follow-up was used to record the date of death only. The database includes patients seen at Centro di Riferimento Oncologica National Cancer Institute, Aviano, Italy, between 1985 and 2012, and between 1999 and 2012 in the other participating centers.

Pericardiocentesis was performed using the Seldinger technique and inserting a pigtail catheter in the pericardial space. After drainage, the catheter was left in place until no significant amount of fluid was drained.

For the creation of a pericardial window, left anterior minithoracotomy (4-5 cm) technique was used under general anesthesia. Patients were placed in the left lateral decubitis position. Each patient's chest was opened between the fourth and fifth intercostal spaces. A 4 × 4 cm or 5 × 5 cm portion of the left pericardium was excised. Fluid and pericardium sample was sent for histologic examination. A drainage tube was inserted into the pleural space and left in place for the following 3 to 4 days.

A scoring system, including both the amount of effusion and the size of the neoplastic pericardial masses was used to assess the disease at presentation and the outcome of the treatment, as already described.[7] Extent of effusion was graded (effusion score) such that 0 = no effusion, 1 = < 1 cm, 2 = 1 to 2 cm, 3 = 2 to 3 cm, and 4 = > 3 cm mean separation on apical view (or at CT scan). Mass score was graded such that 1= a single mass < 2 × 2 cm; 2 = multiple masses, or a single mass > 2 × 2 cm or superficial infiltration; and 3 = tumor encasement or transmural infiltration.

The outcome was considered at the last available follow-up or at the time when a new treatment (first or new pericardial drainage or pericardial window after drainage) was chosen because of worsening, relapse, or incomplete response. The response was classified as complete response (no more pericardial effusion or masses; score = 0), partial response (reduction of the total score, without requiring further treatments), stable disease (unchanged total score), or progressive disease (increased total score).

Patients who had partial or complete response were considered responders, whereas those with stable disease or progression were considered nonresponders.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 13 (IBM-SPSS Inc, Armonk, NY). Descriptive statistics were given as mean ± standard deviation, median, or number (percent). The χ^2 test was used to compare the rate of responders in the groups and for post hoc analysis. Forward stepwise logistic regression analysis (Wald method) was used to determine the variables affecting response. Kaplan-Meier survival analysis was performed to determine survival in the groups.

RESULTS

Our preliminary report included 175 patients (56.6% male) with a mean age of 54.21 ± 14.26 years (range, 15-84.9 years), from the cardiology, cardiology/oncology, surgery, and thoracic surgery departments of 8 centers from 3 different countries. Most of the patients were enrolled from the cardiology/oncology department (34.3%), followed by surgery (29.1%), thoracic surgery (20%), and cardiology (16.6%).

Gender distribution, mean age, and mean follow-up duration was similar for all groups ($P > .05$). The types of cancer were lung cancer in 89 patients (50.9%), breast cancer in 26 patients (14.9%), lymphoma/leukemia in 26 patients (14.9%), and other types of cancer in 34 patients (19.3%). Although there was a somewhat even distribution regarding cancer types in Group A, most of the patients in Group B and C had lung cancer. The demographic characteristics and outcome of the patients are given in Table 1. Overall, 22.3% of patients (n = 39) were in Group A, whereas 42.9% (n = 75) and 34.9% (n = 61) of patients were in Group B and Group C, respectively.

The effusion was <1 cm in only 16% of patients, and more than half of patients (50.9%) had a single mass < 2 × 2 cm (mass score = 1). The extent of effusion (effusion scores) and patients' mass scores are given in Table 2. An effusion score ≥ 3 was present in 6 patients in Group A, in 56 patients in Group B, and in 31 patients in Group C. In Groups B and C, pericardial drainage in

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