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HAL Id: hal-03491196
https://hal.science/hal-03491196
Submitted on 22 Aug 2022

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Les injections intrapéricardiques de bléomycine préviennent la récidive des épanchements péricardiques malins : série de 46 cas et analyse de la littérature

Intrapericardial bleomycin instillation prevent recurrence of malignant pericardial effusions: series of 46 cases and comprehensive literature review

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Author contributions statement
All authors cited in this manuscript (A. LAMBERT, J. SALLERON, A. KIEFFER, P. RAYMOND, L. GEOFFROIS, C. GAVOILLE) had a meaningful contribution to the study and the article.
A. LAMBERT: Conception of the work, data collection, data interpretation, drafting the article, final approval of the version to be published
J. SALLERON: data analysis
A. KIEFFER: critical revision of the article
P. RAYMOND: images and video of the procedure
L. GEOFFROIS: critical revision of the article, final approval of the article
C. GAVOILLE: conception of the work, final approval of the article
Abstract

**Introduction:** Malignant pericardial effusion is a severe complication of lung and breast cancer. The median survival is less than 4 months and recurrences occur in about 40% of cases. Systemic chemotherapy and/or local treatments are necessary, even if there is no consensus. **Methods:** We collected data from patients in our center from 1997 to 2016 who received at least one intrapericardial instillation of bleomycin (60 mg). At the same time, we conducted a review of the relevant literature on the subject. **Results:** We included 46 patients in the analysis. Median survival was 2.6 months [95% CI: 1.7;4.7]. Overall survival was 49% [33%;63%] at 3 months and 28% [15%;42%] at 6 months. In the lung cancer subgroup, overall survival was 18% [3%;44%] at 3 months. In the breast cancer subgroup, overall survival was 73% [44%;89%] at 3 months and 46% [21%;69%] at 6 months. **Discussion:** The best response rates in the literature are obtained with local instillation of bleomycin or cisplatin. Malignant pericardial effusions in breast cancer patients had a better prognosis. This is certainly related to the prognosis of the underlying disease. We have not found an increase in overall survival with intrapericardial chemotherapy injections, but preventing recurrence of malignant pericardial effusions is a benefit in itself, thus avoiding a lethal complication. **Keywords:** pericardial effusion, malignant, lung, breast, cancer.

Résumé

**Introduction :** L’épanchement péricardique malin est une complication sévère des cancers du poumon et du sein. La survie médiiane est de moins de 4 mois et les récidives sont présentes dans environ 40% des cas. La chimiothérapie systémique et/ou les traitements locaux sont nécessaires, malgré l’absence de consensus. **Méthodes :** Nous avons recueilli les données des patients de 1997 à 2016 dans notre établissement qui ont bénéficié d’au moins une injection intrapéricardique de bléomycine (60mg). Parallèlement, nous avons réalisé une analyse de la littérature pertinente sur le sujet. **Résultats :** Nous avons inclus 46 patients. La survie médiane était de 2,6 mois [IC 95% : 1,7 ;4,7]. La survie globale était de 49% [33% ; 63%] à 3 mois et de 28% [15% ; 42%] à 6 mois. Dans le sous-groupe cancer du poumon, la survie globale était de 18% [3% ; 44%] à 3 mois. Dans le sous-groupe cancer du sein, la survie globale était de 73% [44% ; 89%] à 3 mois et de 46% [31% ; 69%] à 6 mois. **Discussion :** Les meilleurs taux de réponse dans la littérature sont obtenus avec une injection locale de bléomycine ou de cisplatine. Les épanchements péricardiques malins avaient un meilleur pronostic dans le cancer du sein, ceci étant probablement dû au pronostic de la maladie sous-jacente. Nous n’avons pas retrouvé d’augmentation de la survie globale grâce aux injections intrapéricardiques de chimiothérapie, mais prévenir la récidive des épanchements péricardiques malins est un bénéfice en soi, évitant ainsi une complication létale. **Mots clés :** épanchement péricardique, malin, poumon, sein, cancer.

Introduction

Malignant pericardial effusion (MPE) is a common complication of lung cancer and, to a lesser extent, breast cancer [1–3]. Cardiac tamponade and pleural effusion are often one of the
first clinical symptoms. MPE is associated with a median survival of less than 4 months [4]. The specific treatment depends mainly on the type of the primary cancer. Chemosensitive cancers tend to be treated with systemic treatment when local treatment is preferable for less chemosensitive tumours [5]. Nevertheless, various techniques (i.e. pericardiocentesis or pericardial window and pericardiotomy for surgical approach) remains controversial. Systemic chemotherapy and local chemotherapy with antineoplastic and/or sclerosing agents are also available. According to the European Society of Cardiology, pericardiocentesis could be performed in a patient with pleural effusion without tamponade and associated with the use of a cytotoxic or sclerosing agent to prevent recurrence [6]. For example, C. Labbé et al. retrospectively compared pericardiocentesis and pericardiotomy in 61 patients from 2004 to 2013 in Canada and concluded that pericardiotomy gave better results for the prevention of recurrences (94.7% vs 69.0%) with similar tolerance and overall survival [7]. Conversely, A. Ciuche et al. in their study of 46 patients showed that minimally invasive techniques were the most effective and most frequent for pericardial drainage [8]. Surgical interventions when used alone are not effective enough to prevent recurrence, which occurs in about 40% of cases [9]. An associated treatment must be initiated. Several options are available, such as systemic or local treatments, sometimes combined [10]. Local treatment has been discussed for years without consensus. Sclerosing and/or antineoplastic agents such as bleomycin, doxycycline, 32P-colloid, carboplatin, cisplatin or thiotepa have been used. For example, bleomycin and doxycycline were compared in a study of 27 patients who concluded that the efficacy of the two molecules was equal, but that the toxicity of bleomycin was significantly lower [11]. Good tolerance to bleomycin was confirmed in 2009 when Kunitoh et al. conducted a randomized trial to compare bleomycin instillation after pericardial drainage with pericardial drainage alone. There was no difference in overall survival [12], but the authors pointed out that bleomycin instillation appeared to be safe and effective in controlling MPEs.
For these reasons, bleomycin instillation following pericardial drainage has remained a standard procedure in our institution. The purpose of this study was to evaluate the impact of bleomycin as local treatment in patients with malignant pericardial effusion secondary to breast and lung cancer, mainly through a series of cases treated in our centre. In the meantime, we conducted a literature review.

Methods

Inclusion criteria

All patients in our centre from 1997 (first known procedure) to 2016 who underwent bleomycin instillation for malignant pericardial effusion with a life expectancy greater than 30 days were included retrospectively. The choice of treatment was left to the physician’s preference, but in all cases the patient had at least one grade-2 symptom of pericardial effusion (dyspnea, chest pain, heart failure and of course cardiac tamponade). According to the guidelines, all patients received at least one instillation of 60 mg of bleomycin locally followed by 50 mL of standard saline to clean the infusion tube after a pericardial drainage (Figure 1). The catheter was clamped for 24 hours, then reopened to evacuate the chemotherapy and finally removed by the surgical team immediately afterwards. All patients were treated with palliative intent and followed until progression and death. Follow-up included clinical examination, cardiac ultrasound and blood tests.

Age, date of death, sex, date of instillation, primary cancer, number of instillations and recurrence of the effusion were collected and analyzed.

The institution review board approved this observational study, informed consent was obtained when available (most patients were deceased at the time of data collection), and this study was approved by the French Data Protection Authority ("Commission Nationale de
l’Informatique et des Libertés”). The investigation conforms with the principles outlined in the Declaration of Helsinki” (Br Med J 1964; ii: 177).

**Literature review**
A literature search using the PubMed National Library of Medicine Interface was conducted using following search terms ‘pericardial effusion AND cancer’, ‘malignant pericardial effusion’, ‘neoplastic pericardial disease’, ‘pleural effusion AND cancer’, ‘intrapericardial treatment’ and ‘intrapericardial bleomycin’ which was limited to the English language from 1996 to present. The references of these manuscripts also made it possible to identify relevant secondary sources. All case reports and studies with a small number of patients (N<5) were rejected.

For each study, the number of cases, the primary neoplasm and treatments were collected. Due to the heterogeneity and difference in data collected between studies, only these follow-up data were collected: Overall survival, time to recurrence and survival at one and two years.

**Statistical analysis**
Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC 25513). Qualitative parameters were described with frequency and percentage; quantitative parameters with median and range. Overall survival was defined as the time interval between the first bleomycin instillation treatment and the date of death. Overall survival was described using the Kaplan-Meier method. The datasets analyzed during the current study are available in the Figshare repository under CC BY license at


**Results**
46 patients were included in the analysis. 36 women were included (78%) and the median age was 58 years (min=21; max=72). 12 (26%) patients had lung cancer, 17 (37%) breast
cancer and 18 (37%) other primary cancer (gastric, ovarian, sarcoma, thymoma, rectal, bladder, renal and esophagus). The distribution of the initial location of the tumours is reported in Table 1. 3 patients had an unknown primary cancer but considering the histology (adenocarcinoma) and clinical evolution, they were probably lung cancers.

We observed an isolated recurrence of pericardial effusion after a first bleomycin instillation in a patient who received a second bleomycin instillation 6-month apart.

The median survival was 2.6 months [95% CI: 1.7;4.7]. Overall survival was 49% [33%;63%] at 3 months and 28% [15%;42%] at 6 months. In the lung cancer subgroup, overall survival was 18% [3%;44%] at 3 months. In the breast cancer subgroup, overall survival was 73% [44%;89%] at 3 months and 46% [21%;69%] at 6 months (Figure 2). Local control of MPE was good, as only one patient had a recurrence and had to be treated twice with intrapericardial bleomycin. No symptoms of recurrence have been reported in other patients. For all patients, death was due to an overall progression of cancer unrelated to MPE.

**Literature review**

14 studies from a literature search through PubMed were included and compiled in Table 2. Among all studies retrieved, two thirds of the patients presented a control of MPE regardless of the treatment (between 68 and 100% of the patients). The best response rates are with bleomycin and cisplatin as in Lestuzzi *et al.* [10] and Celik *et al.* [13] studies. However, the response rate was not reported in every study. Furthermore, recurrences of MPE after drainage alone is up to 40% [9].

The median OS for all patients was between 2.8 and 8.9 months and varies according to the initial location of the cancer. Dempke *et al.* reported an even slightly better median OS of 9.3 months for patients who benefited from two installations [14]. For breast cancer, the reported
median OS was between 9 and 11 months. For lung cancer, the reported median OS was between 2.8 and 4.5 months.

Discussion
In this retrospective study, we noted that MPE remains a serious complication of cancer and no significant progress have been made during the past decades. MPE is a rare event and happens more often in lung and breast cancers. Other locations are even rarer and do not allow assumptions to be made. Our results are consistent with the literature.

Considering the response to treatment, our study is similar to most of the studies retrieved, which is between 68 and 100% of the patients. The recurrences after drainage alone in the literature are up to 40%, but also casts doubt on the efficiency of an associated systemic treatment. The best results seem to be obtained with the combination of local chemotherapy and drainage, such as in our study with only one recurrence (N=1/46 with renal carcinoma).

In our study, results are very different according to the initial location of the cancer. In the lung cancer subgroup, the overall survival was 18% [3%;44%] at 3 months in our study. In the breast cancer subgroup, the overall survival was 73% [44%;89%] at 3 months and 46% [21%;69%] at 6 months (Figure 2). Bischionitis *et al.* in 2000 found a median OS of 330 days (15-1040+) with 5 patients alive after one year and 2 patients alive after two years out of 19 patients with breast cancer [15]. They treated those patients with pericardiocentesis and thiotepa. In our study, 4/17 patients were still alive after one year. Without any doubt, systemic chemotherapy had an impact on overall survival and probably on MPE recurrence, but we couldn’t show any difference for those recurrences as it didn’t occur in any patients with breast or lung cancer.

Local chemotherapy with cisplatin are often preferred for MPE secondary to lung cancer [16,17]. The choice of the chemotherapy molecule in local treatment is guided by the
experience and the habits of each centre but there is no comparative trial to assess which molecule is the best or which regimen is recommended based on cancer location. In the absence of scientific data in this field, it can be assumed that a molecule effective in systemic treatment can also be effective in intrapericardial chemotherapy, but it remains to be demonstrated. Furthermore, a molecule without efficacy at the systemic level could still have an interesting local sclerosing property.

A comparative study between cisplatin and bleomycin for MPE with sub-analysis for lung and breast cancer would be useful but considering the small number of events, all efforts must first be made to show a benefit of intrapericardial instillation concerning recurrences, whatever of the molecule.

Looking more particularly at the initial location of the cancer, MPEs in breast cancer patients had a better prognosis than those in lung cancer patients. This is consistent with the initial prognosis of these diseases. In France, according to the InVS (Institut de Veille Sanitaire) and the Institut National du Cancer, patients with breast cancer have a 5-year survival rate of 87% against 17% for lung cancer (all stages included). According to the National Cancer Institute in the US, stage IV breast cancers have a 5-year survival of 22% as opposed to about 1% for stage IV lung cancers. This gap between both diseases is also found in our study with an overall survival of 73% [44%;89%] at 3 months for breast cancer and 18% [3%;44%] at 3 months for lung cancer. Even though the study population and methodology are different, Lestuzzi et al. (2011) showed that survival for lung cancer was significantly better after combined (local + systemic) chemotherapy (p < 0.001) [10]. 12/53 patients (23%) in this subgroup survived more than 1 year. The overall response rate was higher with intrapericardial cisplatin than with other agents (98% vs 80%, X² = 7.69, p < 0.01) [10]. In another way, Maisch et al. in a study similar to ours, including breast and lung cancer but
with cisplatin, found a mean survival of 2.8 (+/- 1.3) months, which is almost identical to our median survival time of 2.6 months [95% CI: 1.7;4.7] [18].

A major bias in all of these studies is the variation in the protocol for drainage and then administration of chemotherapy. There was no consensus on the surgical technique. Pericardiocentesis followed by local chemotherapy may be as effective as a pericardiotomy or pericardial window with systemic chemotherapy plus local chemotherapy, but probably with fewer side effects. Moreover, all these results are probably conditioned by the technical facilities of each centre. Smaller centres may not have a cardiac surgeon easily available. These are the questions that need to be answered by a prospective study. Such a study will not be easy to implement because MPE is a rare event. A multi-centre approach is needed with respect to the small number of expected inclusions per centre.

To conclude, in our study, medical treatment of MPE did not increase the expected overall survival of these patients. However, we believe that medical treatment of MPE prevents its recurrence and therefore allows us to expect an overall survival close to that initially expected for the underlying disease.

**Figure legend**

Figure 1. Intrapericardial bleomycin instillation procedure

Figure 2. Overall survival: whole population (N=46) and patients with breast (N=15) and lung (N=11) cancers

**Funding**

There was no funding for this study.

**Acknowledgement**

None

**Conflict of interest**
References


Table 1: Distribution of the initial tumour locations of the 46 patients.

<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency (N)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>17</td>
<td>36.96</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>26.09</td>
</tr>
<tr>
<td>Ovarian</td>
<td>5</td>
<td>10.87</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
<td>4.35</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
<td>2.17</td>
</tr>
<tr>
<td>Gastric</td>
<td>1</td>
<td>2.17</td>
</tr>
<tr>
<td>Esophageal</td>
<td>1</td>
<td>2.17</td>
</tr>
<tr>
<td>Rectal</td>
<td>1</td>
<td>2.17</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
<td>2.17</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>2.17</td>
</tr>
<tr>
<td>Thymoma</td>
<td>1</td>
<td>2.17</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>6.52</td>
</tr>
<tr>
<td>Study (year)</td>
<td>No. of cases</td>
<td>Primary neoplasm</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Celik et al. (2014)</td>
<td>175</td>
<td>Lung (N= 89), Breast (N= 26), Others (N= 60). Systemic CT +/- P or W (Cisplatin, Bleomycin and Thiotepa)</td>
</tr>
<tr>
<td>Lestuzzi et al. (2013)</td>
<td>264</td>
<td>Lung (N=146), Breast (N=29), Others (N=89). Systemic CT, Local CT, P, W (Cisplatin, Bleomycin and Thiotepa)</td>
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<td>Lestuzzi et al. (2013)</td>
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<tr>
<td>Lestuzzi et al. (2011)</td>
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<td>Oida et al. (2010)</td>
<td>7</td>
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<td>Maisch et al. (2010)</td>
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<td>Lung (52%), Breast (19.0%), Others (29%). Local CT (Cisplatin)</td>
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<td>Kunitoh et al. (2009)</td>
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<td>Martinoni et al. (2004)</td>
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<tr>
<td>Mortya et al. (2000)</td>
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<td>Lung</td>
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<td>Dempke et al. (1999)</td>
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<td>Breast (N= 23), Lung (N= 8), Others (N= 5). Local CT</td>
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<tr>
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<td>-----------------------</td>
</tr>
<tr>
<td>Colleoni et al. (1998)</td>
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<tr>
<td>Tomkowski et al. (1997)</td>
<td>46</td>
<td>Lung (N=46)</td>
</tr>
</tbody>
</table>

CT= chemotherapy, P= pericardiocentesis, W= pericardial window.