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ORIGINAL ARTICLE

Intrapleural paclitaxel for malignant pleural effusion from ovarian and breast cancer: a phase II study with pharmacokinetic analysis

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Abstract
Introduction Malignant pleural effusion (MPE) is a frequent complication in many types of tumors diminishing the patient's ability to perform activities. Despite various studies on talc treatment, some doubts about its safety and effectiveness remain, so the search for a more ideal intrapleural agent continues. We analyzed the effectiveness and safety of intrapleural paclitaxel in ovarian and breast cancer patients.
Patients and methods The primary endpoint was overall response rate (ORR); secondary objectives included time to progression (TTP), overall survival (OS) and safety of intrapleural paclitaxel. Pharmacokinetics of the drug was also analyzed.
After drainage of pleural effusion and lung re-expansion, paclitaxel 120 mg/m^2 diluted in normal saline was infused through a preinserted catheter which was immediately closed and reopened 24 h later. Blood and pleural fluid samples were collected 1, 4 and 24 h after the end of paclitaxel instillation. When MPE was less than 200 ml/24 h the catheter was removed. Chest radiographs were performed at the beginning of intrapleural paclitaxel, at 1 and 2 months later or with clinical deterioration.
Results We enrolled 18 patients with recurrent MPE: 11 with ovarian cancer and 7 with breast cancer. ORR was 77.8% at 1 month and 88.8%. at 2 months. Median TTP was 5.5 months (CI 95% 0.9–10.1) and median OS was 8.9 months (CI 95% 0.1–17.6). Patients achieving a complete response obtained a statistically significant longer survival than did patients with partial response or progressive disease. Chest pain, fever, and dyspnea were the most frequent side effects. Intrapleural paclitaxel concentrations were very high (mean ± SD = 478 ± 187 mg/l) and declined slowly (mean 24 h reduction ~30%). Detectable but low taxol plasma levels were found in most patients (mean ± SD = 0.045 ± 0.073 mg/l).
Conclusion Intrapleural paclitaxel is a safe and effective palliative treatment for MPE from breast and ovarian cancers and may be integrated with systemic chemotherapy.

Keywords Malignant pleural effusion · Paclitaxel · Ovarian cancer · Breast cancer · Chemotherapy

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Introduction

Pleural effusion is conventionally defined as an abnormal accumulation of fluid in the pleural space. The presence of malignant cells in the pleural fluid establishes the diagnosis of malignant pleural effusion (MPE), a common complication in metastatic cancer. Many hypotheses exist regarding the pathogenesis of MPE in cancer; an MPE can occur when cancer cells infiltrate the pleura, obstruct the lymphatic vessels, and express growth factors, such as

vascular endothelial growth factor (VEGF), which increase vascular permeability and capillary leakage [1].

Although there have been no epidemiologic studies, the incidence of MPE is estimated to be more than 150,000 new cases per year in the United States and 40,000 new cases in the UK [2]. MPEs are most frequently produced by carcinomas of the lung (~37%), breast (~25%), and ovary (~10%). Other causes include malignancies of the genitourinary (7%) or gastrointestinal tract (9%) and lymphoma (10%) [3].

MPE is associated with poor prognosis: median survival following diagnosis is only 4–6 months. MPE management aims to provide durable relief from the distressing symptoms of dyspnea, cough, and chest pain, that greatly compromise patient's quality of life. However, control of malignant pleural effusions is often difficult and inadequate. The most widely used therapeutic approach is pleural effusion drainage followed by instillation of chemical and biological sclerosing agents or by mechanical abrasion. This medical procedure, named pleurodesis, creates a local inflammation with fibrosis and consequent symphysis of the pleura layers, thereby preventing recurrence of the effusion. To date, there is still controversy about which sclerosing agent to use for effective pleurodesis. Many chemical agents have been tested, including bleomycin, doxycycline, tetracycline, and talc. Sterile talc is now recognized as the standard choice for MPE management, although there are reservations due to potential risk of pneumonitis and ARDS (Adult Respiratory Distress Syndrome) following intrapleural talc instillation [4]. Intrapleural chemotherapy with cytotoxic agents has the added advantage of treating the underlying malignancy while controlling effusion. Several chemotherapy agents, such as docetaxel, cisplatin, and cytarabine have been used for intrapleural treatment in patients with MPE [5].

Paclitaxel has a well documented high level of intrinsic activity against lung, breast and ovarian cancers; in addition, this non-water-soluble anticancer agent possesses the proper characteristics for a safe and efficient intrapleural administration. Indeed, its large molecular weight determines a slow clearance rate from the intrapleural cavity, resulting in a longer period of exposure of cancer cells to the taxane. There is still little data available regarding intrapleural paclitaxel injection. Prior experience in patients with lung and breast tumors has demonstrated that paclitaxel may be a useful agent for the treatment of malignant pleural effusion with a low toxicity profile and high local efficacy [6, 7]. In particular, in a phase II trial, Perng et al. [6] demonstrated that intrapleural paclitaxel 125 mg/m^2 is effective with low systemic toxicity in patients with MPE. For all these reasons and to minimize toxicities, we analyzed the effectiveness, safety and pharmacokinetics of intrapleural paclitaxel 120 mg/m^2 in patients with recurrent MPE from ovarian and breast cancers.

Materials and methods

Patient selection

This study was a phase 2, open-label, single-arm, single-institution trial. All patients gave written, informed consent, and the protocol and the consent form were approved by the Independent Ethics Committee of the Istituto Oncologico Veneto. Patients were eligible for this study if they had recurrent, symptomatic, cytologically or histologically proven malignant pleural effusion of ovarian or breast cancer; no prior intrapleural therapy was allowed. Radiotherapy, systemic chemotherapy and hormonal therapy were also not allowed within 4 weeks prior to trial entry. Other inclusion criteria were evidence of expansion of the lung after fluid drainage and absence of bronchial obstruction and/or fibrosis preventing lung expansion; age >18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; predicted survival of >1 month; adequate renal function (creatinine <120 μmol/l), adequate blood cell counts (neutrophil count >1.5 × 10^9/l, platelet count >100 × 10^9/l), and adequate hepatic function (total bilirubin ≤1.5 mg/dl and transaminase levels ≤twice the upper limit of the normal value).

Patients were ineligible if they had a history of cardiac disease, obstructive jaundice or surgery within the previous month, bilateral pleural effusion (because of the danger of inserting two chest tubes at the same time and the difficulty of assessing the response to treatment), pericardial effusion or brain metastases. No patient had systemic chemotherapy within 1 month following intrapleural chemotherapy.

Treatment protocol

All patients had a pre-drainage baseline posteroanterior and lateral chest radiograph and other imaging as clinically indicated. All patients were required to have a chest tube (8 F). The pleural effusion was drained to dryness initially by gravity and followed if necessary by suction from a wall-mounted suction pump using a pressure of 20 cm H_2O usually for 12–24 h to achieve complete drainage of the effusion and lung expansion. Subsequently, posteroanterior and lateral chest radiographs were obtained to assure that the fluid had been sufficiently evacuated, no loculated collections remained and the lung had fully expanded. In cases of suspected trapped-lung and loculated collections, a computerized tomography was performed. Thereafter, intrapleural chemotherapy was carried out. All patients received premedication for paclitaxel treatment, including

dexamethasone 20 mg intravenously 12 and 6 h prior to paclitaxel treatment, chlorphenamine 8 mg intravenous infusion 1 h prior to paclitaxel treatment and omeprazole 20 mg intravenous infusion 30 min prior to paclitaxel treatment. Then, paclitaxel 120 mg/m^2 diluted in 200 ml normal saline was infused into the pleural cavity over 15 min. After paclitaxel instillation, the tube was clamped for 24 h and then reopened. The chest tube was removed if post-therapy drainage was <200 ml per day. If this target was not achieved within 72 h after paclitaxel administration, the treatment was repeated. Posteroanterior and lateral chest radiographs were obtained immediately after tube removal to be compared with others obtained 1 and 2 months later, according to the study-specific criteria (see below). A responder identified at the first evaluation (1 month) was able to receive subsequent systemic chemotherapy at the discretion of the investigator.

Pharmacokinetic analysis

The concentration of paclitaxel was examined in blood and pleural fluid samples collected at times 1, 4 and 24 h following completion of intrapleural paclitaxel instillation. Blood samples were centrifuged immediately upon collection and the plasma separated; pleural effusion samples were frozen shortly after being withdrawn; all samples were stored at −20°C until assayed. Paclitaxel concentrations were measured using a reverse-phase high performance liquid chromatographic (HPLC), using carbazole as internal standard and the Kromasil 100-5Phenyl, 250 × 4.6 mm, as stationary phase. The intrapleural pharmacokinetic parameters were obtained with Prism v.3.1 (GraphPad software, San Diego, CA), using a one compartment model. Because of the inconsistent and low plasma levels, no pharmacokinetic model was fitted to plasma data. Peak plasma and pleural fluid paclitaxel concentrations (mg/l) were defined as the highest measured drug levels in those respective fluids. Intrapleural paclitaxel AUCs (Area under the Curve drug concentration–time) were calculated limited to the 24 h drug exposition period using the trapezoidal model.

Response criteria

Response was determined on chest radiographs by observing the level of fluid meniscus overlying the costophrenic or vertebrophrenic angles and was evaluated according to the following criteria: complete response (CR) determined as no reaccumulation of pleural fluid and absence of symptoms; partial response (PR) determined as reaccumulation of fluid to less than 50% of the original effusion level without symptoms requiring repeat drainage; progressive disease (PD) or failure was determined as reaccumulation of effusion greater than 50% of the original level with symptoms requiring repeat drainage.

Toxicity evaluation

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria version 3. Treatment of possible adverse events seen with this drug, such as nausea, emesis, and anorexia was allowed using standard interventions.

Statistical analysis

The primary endpoint was the overall response rate (ORR). Sample size was calculated to reject a 60% response rate in favor of a target response rate of 90%, with a significance level of 0.05 and a power of 90% by using Simon 2-stage design. In the initial stage, a total of 8 assessable patients were evaluated for response. If >5 responses were observed at 1 month, then 9 additional patients would be selected to enter the second stage to achieve a sample size of at least 17 evaluable patients.

Secondary objectives included time to progression (TTP), overall survival (OS) and safety. TTP was calculated from the start of therapy until disease progression or death or to the last day of follow-up if alive. OS was calculated from the start of therapy to the date of death or to the last day of follow-up if alive. The Kaplan–Meier method was used to estimate survival. To assess the prognostic value of response, a log rank test was used. P

Table 1 Patient characteristics

Characteristic	No	%
Patients	18	
Median age (range)	62	(44–74)
ECOG PS		
0	0	0
1	14	77.8
2	4	22.2
Primary malignancy		
Ovarian cancer	11	61
Breast cancer	7	39
Previous chemotherapy	18	100
1 line	2	11
2 lines	6	33
≥3 lines	10	56
Previous systemic paclitaxel		
Yes	14	78
Not	4	12

ECOG eastern cooperative oncology group

PS performance status

values were based on 2-sided testing, and differences with a $P \leq 0.05$ were considered significant.

The analyses were performed on an intent-to-treat basis. Statistical Analyses were performed with SPSS 15 statistical software (SPSS Inc, Chicago, IL).

Results

Patient characteristics

Between October 2006 and March 2009, 18 patients with malignant pleural effusion from breast and ovarian cancers were enrolled in the study. Patient and disease characteristics are shown in Table 1. The median age was 62 years (range 44–74 years); the median ECOG PS was 1 (range 0–2); 11 (61%) patients and 7 (39%) patients had ovarian and breast cancers, respectively. All patients had a previous systemic treatment and undergone therapeutic thoracentesis in the last 4 months before intrapleural paclitaxel. All patients but four with breast cancer had previously received systemic paclitaxel. No patient was administered systemic paclitaxel after intrapleural treatment.

Histology of the primary breast tumor was ductal carcinoma in 3 patients and lobular carcinoma in 4 patients; histology of the primary ovarian cancer was undifferentiated in 1 patient, serous adenocarcinoma in 7 patients, endometrioid adenocarcinoma in 2 patients and clear cell adenocarcinoma in 1 patient.

Clinical efficacy

All patients performed intrapleural paclitaxel and all patients were evaluable for response at 1 and 2 months. Fifteen patients (83.3%) performed a subsequent systemic treatment after 4 weeks from intrapleural paclitaxel. At the time of analysis, all 18 patients had died. The median volume of fluid drained on the 1 day after paclitaxel instillation and pleural effusion drainage was 600 ml, on the 2 day it was 150 ml. Decrease in pleural effusion drainage below 200 ml/24 h was achieved in 1 patient, below 200 ml/72 h in 16 patients. In two patients, paclitaxel was administered intrapleurally twice and both achieved a decrease in pleural effusion drainage below 200 ml/24 h. Chest tube was removed within 5 days in 85% of patients (range 2–7 days).

The ORR at 1 month was 77.8%, at 2 months was 88.8% (see Table 2). At 1 month, CR was seen in 4 patients (22.2%) and PR was observed in 10 patients (55.6%); PD was observed in 4 patients (22.2%). The same patients were evaluated at 2 months: CR was observed in 8 patients (44.4%), PR in other 8 patients (44.4%) and PD in 2 patients. Four of 8 patients who obtained PR at 1 month showed complete response at 2 months; two patients with demonstrated PD at 1 month showed partial response at 2 months (compared to the pretreatment imaging).

The median TTP of the entire population was 5.5 months (CI 95% 0.9–10.1) and the median OS was

Table 2 Response of MPE after paclitaxel intrapleural treatment

	1 month		2 months	
Response	No	%	No	%
Complete response	4	22.2	8	44.4
Partial response	10	55.6	8	44.4
Overall response rate	14	77.8	16	88.8
Progressive response	4	22.2	2	11.2

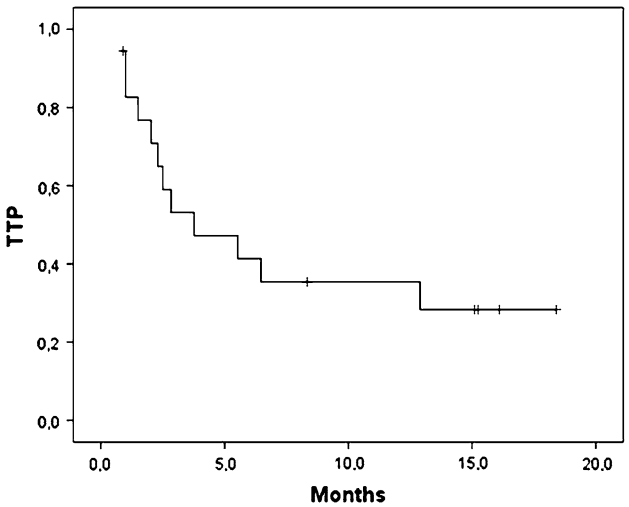

Fig. 1 The median time to MPE progression was 5.5 months (CI 95% 0.9–10.1)

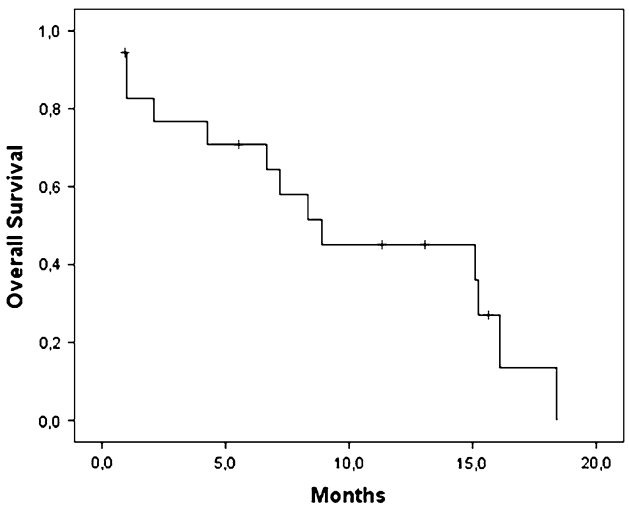

Fig. 2 The median overall survival was 8.9 months (CI 95% 0.1–17.6)

Table 3 Adverse events related to the intrapleural paclitaxel

Complication	No	%
None	4	22
Chest pain	12	67
Grade 1	10	
Grade 2	2	
Fever	10	56
Grade 1	10	
Dyspnea	3	17
Grade 1	2	
Grade 2	1	
Infusion site extravasation	8	44
Grade 2	8	
Fatigue	2	11
Grade 1	1	

8.9 months (CI 95% 0.1–17.6) (see Figs. 1, 2). There were no significant differences in terms of ORR, TTP and OS between the patients with breast cancer and the patients with ovarian cancer ($P > 0.05$).

We performed a log rank test to evaluate the association between the type of response at 2 months and survival: the patients, who achieved complete response, obtained a statistical significant longer survival than did patients with partial response or progressive disease (15.2 vs. 7.2 months, $P = 0.03$).

Toxicity

All patients were assessable for toxicity. Adverse events related to the intrapleural paclitaxel are listed in Table 3. The treatment was generally well tolerated, and no treatment-related death occurred. Moreover, no grade 3–4 adverse events were observed, and 4 patients (22%) experienced no adverse events. Chest pain (67%) and fever (56%) were the most common toxicities related to paclitaxel instillation, although they were easily managed with paracetamol.

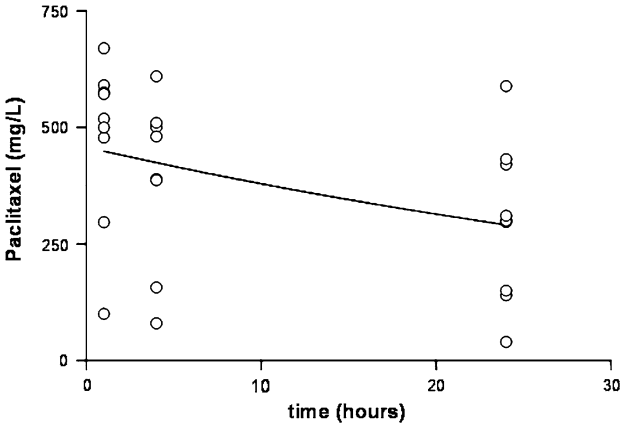

Fig. 3 Intrapleural paclitaxel: individual concentrations (*circles*) and mean decay curve (*line*)

Pharmacokinetic analysis

Intrapleural and plasma samples were collected from 8 and 16 patients, respectively. Intrapleural pharmacokinetic analysis was feasible for all 8 patients (see Table 4). One hour after instillation, the intra-thoracic paclitaxel concentrations were very high and variable, ranging from 100 to 670 mg/l; the median level was 545 mg/l. The volumes of distribution were low, according to the supposed restriction of drug to the pleural cavity. Paclitaxel concentrations showed a slight decrease in the thoracic cavity, with a mean reduction of ~30% after 24-h exposure period (see Fig. 3): drug elimination from the pleural compartment was generally slow and varied among patients, with a mean half-life ± SD of 68.4 ± 65.8 h.

Table 4 Paclitaxel kinetics in pleural fluids and plasma peak levels

Patient (*N*)	Peak IP level (mg/l)	Vd (l)	IP $T_{1/2}$ (h)	IP AUC 0–24 h (mg × h/l)	IP clearance ($l/m^2/d$)	Peak plasma level (mg/l)
1	572	0.31	62.8	11,043	0.26	0
2	576	0.42	26.8	9,506	0.30	0.01
3	670	0.30	160.5	13,910	0.21	0
4	100	2.0	28.4	2,175	1.32	0.22
5	500	0.40	184.5	9,411	0.31	0.07
6	591	0.32	24.1	9,658	0.30	0.05
7	519	0.35	nd	6,429	0.45	0
8	297	0.67	23.7	3,651	0.79	0
Mean ± SD	478 ± 187	0.60 ± 0.58	68.4 ± 65.8	8,222 ± 3,893	0.49 ± 0.38	0.003 ± 0.005

SD standard deviation, *IP* intrapleural

Detectable paclitaxel plasma concentrations were obtained in 12 out of 16 patients (mean ± SD = 0.045 ± 0.073) and were generally low.

Discussion

Breast and ovarian cancers represent one of the most frequent causes of MPE. The prognosis of patients with MPE is poor: patients with breast cancer and MPE commonly live for 1 year, whereas those with primary ovarian cancer have an expected survival of 9 months [8, 9]. A large MPE compromises ability to perform activities of daily living and the most frequent signs are dyspnea, cough, and variable chest pain which may be diffused or localized. Management of MPE is considered palliative because it does not improve survival. The main indication for treatment is relief of dyspnea through evacuation of the pleural fluid and prevention of its reaccumulation. The most widely used local therapy for MPE was tube drainage with intrapleural instillation of sclerosing agents to cause inflammation to prevent fluid reaccumulation.

Sclerosing agents principally consisted of bleomycin, doxycycline, tetracycline, mitoxantrone, and talc; various clinical studies have been undertaken in an attempt to determine the optimal drug for pleurodesis, but adequate comparative trials are too few and the ideal agent remains controversial [3]. Talc, with a success rate of 70–100% appears to be the sclerosant of choice for pleurodesis and a recent meta-analysis showed a significant reduction in MPE recurrence [10]. Its limitations include complications ranging from acute pneumonitis, granulomatous pneumonitis and acute respiratory distress syndrome; however, a prospective cohort study demonstrated that large-particle talc is safer and is not associated with the development of acute respiratory distress syndrome than smaller particles [4].

In recent years, in addition to sclerosing agents, local chemotherapy agents including cisplatin, carboplatin, etoposide, cytarabine [11–14] had been used in intracavitary chemotherapy for MPE with a response rate at 3–4 weeks that ranges from 46 to 100% [15]. The use of intrapleural chemotherapy has the potential advantage of treating the underlying malignancy, controlling the malignant effusion, maximizing the chemotherapeutic treatment of local disease while minimizing systemic toxicity. In particular, paclitaxel, a taxane anti-microtubule agent demonstrating efficacy in the treatment of ovarian and breast cancer, was studied as intrapleural agent by Perng et al. in phase I and II studies [6, 7]. In the phase I study, the authors demonstrated that paclitaxel at a dose level of 175 or 225 mg/m^2 is feasible for intrapleural use; moreover, the authors showed that the mean exposure of the pleural cavity to paclitaxel after intrapleural delivery exceeded that of plasma by approximately 370-fold and the slow intrapleural clearance of paclitaxel meant a significant concentration of paclitaxel persisted within the cavity for more than 96 h after instillation. In our study, the pharmacokinetic data are similar to those obtained by Perng and inter-patient variability was confirmed in both pleural and plasma fluid parameters. Pleural paclitaxel levels were generally very high during the 24 h period of drug exposure, while plasma levels were very low, suggesting limited systemic absorption. In the phase II trial, Perng et al. [6] studied the clinical response and toxicity of intrapleural paclitaxel 125 mg/m^2 performed in 15 NSCLC patients with MPE. Among the 14 patients evaluable at 4 weeks, the effusion control rate was 92.9% and at 8 weeks was 71.4%. Although our patients had different tumors, in our study the ORR was 77.8 and 88.8% at 1 and 2 months, respectively; likely, the higher ORR obtained at 2 months may be due to subsequent systemic chemotherapy performed in almost all patients while it may also be related to the different types of cancer. Thus, these results demonstrate that intrapleural paclitaxel may easily be integrated with systemic chemotherapy enhancing the response to local treatment itself, even if paclitaxel has already been administered as previous systemic treatment. Moreover, we demonstrate that complete response at 2 months from intrapleural paclitaxel is a positive predictor in term of survival, likely improving both quality of life and survival in these patients.

In a recent phase I clinical and pharmacokinetic study, Wang et al. [16] investigated the feasibility, pharmacokinetics, efficacy and toxicity of intrapleural paclitaxel liposome injection in 15 NSCLC patients with MPE; the ORR at 1 month was 90.9% and at 2 months was 72.7%. These results were similar to Perng's study [6]. On the contrary, the toxicity of paclitaxel liposome was much lower: symptoms of diarrhea, anemia, neutropenia, thrombocytopenia, hepatotoxicity, and chest pain were all more severe in Perng's phase II study patients treated with free paclitaxel.

In our study, the toxicity profile was safe and easily manageable. There were no reports of nausea and vomiting among the patients and no patient developed neutropenia compared with 6.7% in Perng's study. On the contrary, in our study more patients reported chest pain (67%) following intrapleural paclitaxel compared with the other study (47%). Moreover, we reported 56% of patients with fever compared with 33% observed by Perng. Likely, these differences are due to greater resident time of the drug into the cavity: 24 h in our study versus only 2 h in the previous study.

In a recent phase I study, Jones et al. [17] analyzed the pharmacokinetic properties, clinical response and toxicity

profile of intrapleural docetaxel, another taxane anti-microtubule agent, in 15 patients with MPE, most of whom had NSCLC. They found a 1,893–6,675-fold higher exposure in the pleural cavity compared with plasma and a similar toxicity profile to previous phase I/II trials using paclitaxel and our study. Constitutional symptoms were noted in 33% of patients, the incidence of anemia was at 13% and no patients developed neutropenia from docetaxel treatment. Regarding efficacy, while it was not a primary endpoint, 90% of patients treated with a single dose of 75 mg/m^2 had a complete response at 3 weeks after treatment. No data are available at 2 months after therapy although median survival was only 3.6 months.

In conclusion, our study is the first prospective study to evaluate the efficacy and safety of intrapleural paclitaxel to treat MPE from ovarian and breast cancers. We show that intrapleural paclitaxel appears to be a useful drug for the treatment of MPE from ovarian and breast cancers. In particular, its efficacy appears greater 2 months after treatment and may be used in combination with systemic chemotherapy. Moreover, patients with a complete response (44.4%) had a statistically significant longer survival time than did patients with partial response or progressive disease. In addition, its toxicity profile appears manageable and safe, with no grade 3–4 adverse events observed. In fact, low taxol plasma levels at 24 h after the treatment suggest limited systemic absorption with few systemic side effects.

In light of these results, intrapleural paclitaxel should be considered as a part of treatment options in patients affected by breast or ovary cancer with MPE providing durable relief from the distressing symptoms that compromise patient's quality of life. However, further randomized studies are needed.

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