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Safety and Feasibility of Intrathoracic Chemohyperthermia after Pleural Cytoreduction: A Single-Institution Experience with 50 Patients and Literature Review

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Abstract

Background: Pleural malignancy treatment produces disappointing results, even with current multimodal therapeutics. Cytoreductive surgery combined with Intrathoracic Chemohyperthermia (ITCH) is an under-evaluated therapeutic option. We aim to investigate the feasibility and the postoperative results of this technique.

Methods: We retrospectively reviewed the postoperative courses of 50 patients who underwent ITCH between 1990 and 2014. Data on histologic type of pleural tumor, type of surgery, ITCH performed, and postoperative course were analyzed.

Results: The operated patients included 19 women and 30 men, with an average age of 55.3 years (range, 21-73 years). Twenty-seven patients had mesothelioma, 9 pleural metastasis of thymoma, and 14 pleural metastasis of other histological type. All patients underwent partial or subtotal pleurectomy, without major anatomic resection. ITCH was performed for over 90 min; at an inflow temperature of <45°C; with mitomycin C, cisplatin, or both. One post-operative death occurred, due to acute respiratory distress syndrome. Post-operative complications included hemorrhage (n=2), pleural abscess (n=1), persistent air leaks (n=2), wound sepsis (n=4), aplasia (n=1), and renal insufficiency (n=1). Average drainage duration was 6.3 days (range, 3-14 days) and average length of hospital length stay was 10 days (range, 6-18 days).

Conclusion: ITCH combined with cytoreductive surgery appears to be a surgical procedure with acceptable mortality and morbidity rates. Its efficiency according to tumor type should be further evaluated, specifically with regard to types and doses of chemotherapeutic agents.

Keywords: Pleural disease; Thoracic surgery; Cytoreduction; ChemoHyperthermia; Morbidity

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Introduction

The last decades have seen more frequent appearances of malignant pleural effusion, mesothelioma, and pleural invasion of thymoma [1]. These malignancies presently have no standard treatment with curative intention and have poor reported survival rates [2,3], particularly for malignant pleural mesothelioma [4]. Current treatment options involve multimodality therapy; however, local control is difficult due to the diffuse and invasive local behavior of these malignant tumors on the pleural surface, and complete resection is almost impossible with the presence of widespread pleural seeding. In spite of these difficulties, pleurectomy/decortication is associated with low morbidity and mortality [5].

A multimodal approach consisting of cytoreductive surgery and intrathoracic chemohyperthermia (ITCH) might improve local tumor control. This procedure offers the theoretical advantage that the tumor is directly exposed to higher drug concentrations, and thus a lower incidence of toxic side effects may be expected. Twenty years ago, we reported a phase I study on the combination of surgery with ITCH for diffusive malignant pleural effusion [6], followed 10 years later by a survival analysis [7]. Over the past 10 years, several surgical teams have described their experience with

Table 1: Population.

Patients conditions	
Cardiovascular	
cardiac arrythmias	n = 4
ischemic heart disease	n = 1
Mean LVEF (Left Ventricular Ejection Fraction)	68,4 % (6,2 ; 54–80)*
Mean FEV1 (Forced Expiratory Volume in 1s)	80,8 % (20,5 ; 48–129)*
Mean renal function	90,2 mL/mn (35,9 ; 41,5–173,3)*
Diagnosis	
Malignant pleural mesothelioma	n = 27
epithelial	*n = 10*
sarcomatoid	*n = 3*
biphasic	*n = 1*
ns	*n = 13*
Thymoma	n = 9
Other	n = 14
Metastatic carcinoma	*n = 8*
Sarcoma	*n = 5*
Malignant solitary fibrous tumor	*n = 1*
Perioperative treatment	
Neoadjuvant chemotherapy	n = 8
Adjuvant treatment	n = 21
chemotherapy	*n = 14*
radiotherapy	*n = 4*
both	*n = 3*

*Values are presented as followed: Mean (Standard Deviation; Min – Max)

using this technique for treating malignant pleural mesothelioma [8], and other histologic types [2,4]. Most have analyzed survival or pharmacokinetics in a cohort not exceeding 30 patients.

The present retrospective study aimed to evaluate post-operative morbidity and mortality of ITCH combined with cytoreductive surgery in a larger patient group than previous studies.

Patients and Methods

We performed an observational single-center study including 50 patients who were consecutively operated in our department of thoracic surgery at the University Hospital of Lyon, France between March 1990 and February 2014. Indication of ICTH was based on surgeon's experience and systematically discussed at an expert multi-disciplinary tumor board. Patient operability criteria were diffusive malignant pleural disease, no evidence of spread beyond the involved hemithorax or extrathoracic metastases, and cardiorespiratory function sufficient to allow the required resection. Patients were considered inoperable if they were older than 75 years, showed renal or myocardial failures, or had central nervous system disease (vascular or neoplastic).

All malignant pleural diseases, except for thymomas, were found during thoracoscopy for preoperative cytological and pathological evaluation. Patients with suspected de novo Masaoka stage IVa thymoma or a thymoma pleural relapse were operated with preoperative pathologic confirmation-except for two patients with pleural relapse who were operated based on clinical and radiological arguments. Patients underwent preoperative complete blood count, renal function tests, electrocardiogram, and whole body scan. Preoperative positron emission tomography was performed in the last seven patients treated. All patients had pulmonary function tests and echocardiogram, and their treatment plans were discussed in a multidisciplinary meeting. Surgery was performed at least one month after the last course of chemotherapy.

ITCH

The procedure was performed under general anesthesia, with the patient in the lateral position, and with a double-lumen endotracheal tube, a venous central catheter, an arterial catheter, and urinary and esophageal temperature sensors. Urinary output was controlled continuously. A thoracic epidural catheter was inserted in all cases. A "prehyperthermia" hypothermia (under 34°C) was induced using ice bags, cold wraps on the legs, and a cooling hat, to offset the systemic temperature rise upon administration of hyperthermic chemotherapy. The extent of surgery was determined according to the disease and the patient's condition under one lung ventilation. The maximal attempt was made to remove all macroscopic tumor by mean of parietal pleurectomy and diaphragmatic and/or pericardium resections when appropriate, according to disease distribution. Formal decortication was required in case of extended visceral pleura component. Otherwise, resection was limited to visceral nodules excision or wedge resections, depending on the size of the nodules.

Before thoracotomy closure, the equipment needed for ITCH was inserted into the pleural cavity. Two 30 French silicone drainages were inserted: one at the top of the cavity (inflow drainage) and one at the cavity bottom (outflow drainage). To obtain optimal temperature control, thermic probes were introduced through chest tube wounds and also inserted with the drainages at the top and the bottom of the cavity, distant from the chest tubes extremities. Then the thoracotomy was closed, the patient was turned to the supine position, and the inflow and the outflow drainages were connected to a sterile closed circuit through which 1.4 L/m^2 of perfusate (isotonic dialysis fluid) was propelled using a roller pump at the rate of 650 mL/min (Cavitherm, Soframedical, Vienne, France). This liquid was heated through a thermic exchanger connected to a heating circuit. Intra- and extrapleural thermic probes were connected to the thermic reader to be monitored continuously. Upon reaching a homogenous intrathoracic temperature of 42°C, the cytotoxic agents cisplatin (CDDP; 35 mg/m^2; maximum dose of 70 mg) and mitomycin C (MMC; 25 mg/m^2; maximum dose of 50 mg) were added as bolus to the perfusion system.

ITCH was performed over 90 min, with a semi-inflated lung that allow sufficient space between the lung parenchyma and chest wall

Table 2: Postoperative course.

Complication	Number
Postoperative death (day 14)	n = 1
ARDS[1]	n = 1
Hemorrhage[2]	n = 2
Empyema	n = 1
Persistant air leaks (>7 days)	n = 2
Wound	n = 4
Pneumonia	n = 1
Venous thrombosis*	n = 0
Atrial fibrillation*	n = 0
Renal insufficiency**	n = 1
Aplasia**	n = 1

(1) Acute Respiratory Distress Syndrome
(2) One required reoperation
*missing data = 2
**missing data = 1

for adequate perfusion, paying close attention to respiratory and hemodynamic functions. The mean maximal inflow temperature was less than 45°C. During ITCH, blood samples were taken twice to determine white cell, red cell, and platelet counts; coagulation; serum proteins; lactic acid; and blood gas. At the end of the procedure, the tubes were disconnected from the perfusion system and were used as standard thoracic drains. After surgery, all patients were admitted to the intensive care unit, where the above-described parameters were again determined throughout the day. Follow-up was performed at 1 month, and then every 3 months in the outpatient clinic. Computed tomography scans were performed every 3 or 6 months depending on the pathology, or when recurrence was suspected. Data were retrospectively collected. We reviewed each patient's comorbidities at the time of surgery, especially their renal, cardiac, and respiratory functions. We also registered the pathologic type of tumor, the use and regimen of neoadjuvant chemotherapy, the type of surgery, and the intrapleural chemotherapy. Complications that occurred within 90 postoperative days, due to surgery or chemotherapy, were recorded and classified following the Common Terminology Criteria for Adverse Events of the National Cancer Institute (NCI classification v4.0, 2009).

Statistical Analysis

Collected data were analyzed using SAS version 9.3. For descriptive data, results were expressed as mean, Standard Deviation (SD), and range. We studied the influence of the following factors on postoperative course: sex, age at surgery >65 years, smoking status, renal (creatinine clearance <60 mL/min) and cardiac (LVEF <70%) functions, preoperative performance status (World Health Organization performance scale), preoperative chemotherapy, pathology, type of surgery, diaphragmatic resection, vascular complication during surgery, parenchymal air leaks at the end of surgery, and type of intrapleural chemotherapy used. Qualitative data were compared using univariate analysis with Fisher's exact test.

Results

Between March 1990 and February 2014, 50 patients underwent a pleural cytoreduction combined with ITCH with MMC and/or CDDP. From March 1990 to October 1995, ITCH was performed with MMC for mesothelioma (n=7) and with CDDP (n=3) for metastatic carcinoma. Following our previously published feasibility study (5), ITCH was performed with both MMC and CDDP for each type of tumor from November 1995 to March 2014 (n=40). The patients included 19 women and 30 men (missing data for one patient), with ages ranging from 21 to 73 years (mean, 55.3 years; SD, 11.5). The underlying conditions were malignant pleural mesothelioma in 27 cases, thymoma in 9 and pleural metastasis of other pathologic type in 14 (Table 1). Eight patients received neoadjuvant chemotherapy. No preoperative radiotherapy was realized.

All patients underwent subtotal parietal pleurectomy, associated with excision of nodules on the visceral pleura (n=4), decortication (n=16), or wedge resection (n=8), without major anatomic resection. Pericardial resection was not required. All procedures were performed by thoracotomy, except one performed by video-assisted surgery (parietal pleurectomy only). Some difficulties were encountered during surgery, including multiple air leaks due to revision surgery (n=5), partial resection of the diaphragm without replacement (n=3), and vascular wound (n=1). No technical problems were encountered during the perfusion period. Table 2 presents the postoperative complications, which included one postoperative death at 14 days after surgery due to Acute Respiratory Distress Syndrome (ARDS). This ARDS occurred one day after surgery, and was probably caused by intraparenchymal diffusion of chemotherapy due to massive air leaks related to extensive decortication. We precise that this patient did not receive preoperative chemotherapy.

The overall morbidity rate was 26%, with the most frequent complication being parietal wound abscess (grade 1) treated with local care (n=4). Only two complications related to intrapleural chemotherapy were observed: one aplasia (grade 3) and one acute renal insufficiency (grade 2) with favorable evolution after corticosteroid and immunosuppressive treatments. Dialysis was not required. Overall, 10 patients presented complications classified as NCI grade 1 or 2, and 3 patients presented complications superior to NCI grade 3. Mean drainage duration was 6.3 days (range, 3-14 days). Mean duration of stay was 44 hours (range, 24 hrs to 336 hrs) in the intensive care unit, and 10 days (range, 6-18 days) in the hospital. Univariate analysis revealed that male gender was the only factor related to postoperative complication (P=0.015). Preoperative chemotherapy was not related with higher post-operative complication rate.

Discussion

Our present results suggest that ITCH combined with cytoreductive surgery is an acceptable technique, showing a post-operative morbidity of 26% and mortality of 2%. Most observed postoperative complications were mild or moderate (n=10), with 6% being severe, including one ARDS leading to death, one postoperative hemorrhage requiring reoperation, and one instance of chemotherapy toxicity. It appears that chemohyperthermia is not associated to higher morbidity or mortality than pleurectomy/decortication alone [5].

Compared with the findings of our prospective study in 2003 [7], our present results show similar results with a cohort twice as large. A previous study included as many patients as in ours and was also limited to surgery of the pleura (excluding pleuro-pneumonectomy); however, the patients were only treated for Malignant Pleural Mesothelioma (MPM), and the results were focused on survival [8]. Their results showed post-operative mortality (4%) similar to in our study, but post-operative morbidity was not specified. A prospective phase I to II study of the tolerability of dose-escalated cisplatin was conducted in the same center [3]; they investigated 44 patients and reported post-operative morbidity and mortality rates higher than in our present study: 11% mortality, 57% renal toxicity, 11% ARDS, and 32% atrial fibrillation. This difference can likely be explained by the

Table 3: Specificities of ITCH in the literature.

Study	Year	Number of patients	Primary tumor	Chemotherapy	Doses (mg/m²)	Duration (minute)	Flow (mL/min)	Volume (mL)
Matsuzaki	1995	19	lung (n = 12) other (n = 7)	cisplatin	200	120	1000	2000
Ratto	1999	10	MPM*	cisplatin	100	60		
De Bree	2001	14	MPM (n = 11) TEMT** (n = 3)	cisplatin + doxorubicin	80 15 - 25	90	1000	ns
Van Ruth	2002	24	MPM; TEMT; thymoma	cisplatin + doxorubicin	80 15 - 35	90	1000	ns
Sugarbaker	2006	44	MPM(n = 44)	cisplatin	50 - 250	60		
Ried	2012	16	MPM (n = 8) TEMT (n = 8)	cisplatin	100 - 150	60	1200 - 1500	2000 - 4000
Yellin	2012	35	TEMT (n = 35)	cisplatin + doxorubicin	100 50-60	60	1000 - 2500	1500 - 3500
Isik[33]	2013	19	lung (n = 11) other (n = 8)	cisplatin	300	60	1500 - 3200	1000 - 1200
Current study	2013	50	MPM (n = 27); TEMT (n = 9); other (n = 7)	cisplatin + mitomycin C	35 25	90	650	1000 - 2000

*MPM: Malignant Pleural Mesothelioma
**TEMT: Thymic Epithelial Malignant Tumor

cisplatin dosage (50-250 mg/m² *vs.* 25 mg/m² in our study) and mean age of the patients at operation (71 years *vs.* 55 years in our study). To our knowledge, two other studies with cohorts larger than 20 patients have reported feasibility results [2,9]. Morbidity and mortality were similar to our present findings.

Concerning the technique itself, our approach is somewhat different from that described in other studies. We performed the ITCH once the chest was closed, and with the patient in a supine position. Other surgical teams perform this procedure with the patient in a lateral position [10,11], or with the chest cavity open [3,11]. We preferred to minimize the time that the patient was in a lateral position, considering that the pleural cavity is equally exposed to chemotherapy in the supine and lateral position. Our perfusion duration was 90 min, while others prefer 60 minutes. The 90-min duration was calculated based on the intraperitoneal chemohyperthermia [12], according to which our procedure was initially defined in collaboration with general surgeons.

MMC was one of the first drugs studied for use in pleural and peritoneal cavities [13,14], following the discovery that hyperthermia enhances its *in vitro* cytotoxicity toward hypoxic tumor cells [15]. Studies of MMC in dogs [16] and humans [17] have improved our knowledge of its pharmacokinetics [12], and led to increased use. Although MMC seems to be less efficient than other drugs used with mild hyperthermia [18], it continues to be administered because of its good tolerability in association with cisplatin and its interesting ratio of peak concentrations between the pleural cavity and plasma [19]. Maximum tolerated doses are not defined, and maximum serum concentration is reached 45 minutes after the start of intraperitoneal chemohyperthermia [12,20]. Using an MMC dose of 8 mg/m² (lower than in the present study), Rusch et al. [21] showed that the pharmacokinetics of intrapleural MMC associated with cisplatin are similar to those of intraperitoneal chemotherapy.

Table 3 presents different chemotherapeutic agents used for intrathoracic chemohyperthermia.

Although there is no standard chemotherapy for this application, many teams report the use of cisplatin. Some centers use it alone [3,4,8], others in association with doxorubicin [2,10,11,21]. This practice seems logical, as cisplatin is administered as first-line treatment for thymic epithelial tumors and MPM. Its pharmacokinetics have been investigated after pleural administration associated with hyperthermia [21-23]. Hyperthermia potentiates the *in vitro* cytotoxicity of cisplatin [25]. The first studies were conducted after intraperitoneal administration *in vivo* in animals [24,25], which verified that hyperthermia enhanced its effect *in vivo*, and provided a model for treatment of intraperitoneal malignancies. In humans, Rusch et al. [21] demonstrated that the pharmacokinetics of cisplatin-based chemotherapy are similar to those of intraperitoneal chemotherapy.

To date, there remains no consensus regarding optimal cisplatin dosage. Ried et al. [4] studied the pharmacokinetics, and showed a pharmacological advantage of a high local intrapleural cisplatin concentration, with dosages of 100 and 150 mg/m² used without increasing side effects [26]. However, this study included only 16 patients. In the present study, we administered low doses of cisplatin (25 mg/m²), whereas other teams have successfully administered much higher doses [2,3,26]. Richards et al. [3] performed a phase I to II study of ITCH with dose-escalated cisplatin (50 to 250 mg/m²), associated with administration of sodium thiosulfate to prevent from renal toxicity, in 44 patients with malignant pleural mesothelioma. They report 48% renal toxicity of grade 1 or 2 and 9% higher grade renal toxicity. Previous reports suggest that severe complications, especially renal complications, are not increased with a cisplatin dose of less than 150 mg/m². As in the present study, all prior studies report perioperative hyperhydration with these doses of cisplatin. The use of sodium thiosulfate is an interesting method, but it is not available in every country. In the current study, we maintained the doses beyond the duration of our initial prospective study [7] due to the good tolerance and theoretical benefit [6]. We acknowledge that we could administer higher doses with adapted perioperative hyperhydration, and we plan to make this change in the future, without exceeding a total dose of 100 mg. Ried et al. [4] showed that the mean peak of cisplatin in the serum was reached after 1 hr [26], confirming other reports [21-23], and suggesting a minimal chemohyperthermia duration of 1 hr.

Doxorubicin, another drug used in association with cisplatin [2,10,11], has a high molecular weight and hydrophilic properties, and thus exhibits slow peritoneal clearance and may act on tumor cells at higher concentration, and therefore with increased direct cytotoxic activity, like MMC and cisplatin. Studies of hyperthermic intraperitoneal doxorubicin administration in murine models [27,28] and humans [29] have confirmed this theoretical advantage. Transposition to the pleura showed comparable results [30,31]. Van Ruth et al. [11] studied the pharmacokinetics of doxorubicin

in association with cisplatin after pleural cytoreductive surgery and ITCH. As expected, they report adherence of a substantial fraction of the drug to superficial structures within the thoracic cavity (i.e., intercostal muscles). However, the penetration of doxorubicin in tumors is limited to a few millimeters [27], highlighting the need for cytoreduction. Doses from 15 to 35 mg/m^2 were associated with no cardiotoxicity, and with one case of nephrotoxicity that was attributed to cisplatin and inappropriate hydration. Interestingly, the plasma concentration of doxorubicin and cisplatin reached almost steady-state levels within 90 min. For the use of doxorubicin, the duration of chemohyperthermia could be determined based on these data.

The combined use of cisplatin with other chemotherapy is neither systematic nor studied as thoroughly as the use of cisplatin or other chemotherapeutic agents alone. Cameron et al. [32] recently concluded that the basic scientific foundation of hyperthermic chemotherapy perfusion is insufficient, and conducted an *in vitro* evaluation of MPM. They showed that intrapleural chemotherapy produced a modest effect, but was most effective when two drugs were combined. To our knowledge, only two chemotherapeutic agents have been associated with cisplatin in pharmacokinetics studies: MMC [21] and doxorubicin [11]. In our experience, we have only used MMC in association with cisplatin, because its effectiveness and pharmacokinetics are correctly controlled under hyperthermia conditions, given its intraperitoneal use. However, we would prefer to use doxorubicin in the specific case of thymic epithelial tumors, as it is administered intravenously for this indication [32]. Other centers [2,11] have reported its use with encouraging results.

The potential clinical benefit of ITCH in association with cytoreductive surgery on local control and overall survival has yet to be demonstrated, and clinical data are limited to retrospective series. However, encouraging results have been published. Richards et al. [3] showed significantly longer survival for patients with malignant pleural mesothelioma submitted to high doses (175-250 mg/m^2) of cisplatin with ITCH as compared to low doses (50-250 mg/m^2), with median survival of 18 versus 6 months. In a small cohort of patients with malignant pleural effusion, Isik et al. [34] recently showed that cytoreduction combined with ITCH (cisplatin 300 mg/m^2) significantly improves survival compared to in previous patients who received pleurectomy or talc pleurodesis. Moreover, in a retrospective study, Sugarbaker et al. [8] showed that selected patients with MPM submitted to surgery and ITCH with cisplatin had significantly longer interval to recurrence and overall survival than patients who underwent surgery alone. Recently, we reported a mean disease-free survival of 42 months and a five year survival of 86% in a cohort of 19 patients treated by cytoreduction and ITCH for pleural recurrence of thymoma [35]. However, to date, these series are too small to evaluate long term benefits of ITCH on survival whatever the origin of the pleural invasion. In the future, it will be crucial to standardize practices to promote multicentric prospective studies.

Conclusion

Cytoreductive surgery in combination with ITCH with cisplatin and MMC can be performed with acceptable morbidity and mortality. Complete surgical resection leaving only microscopic residual tumor is essential because the drug penetration depth is limited to a few millimeters. Many problems remain to be solved, and controlled studies are necessary to evaluate the clinical benefit of this therapeutic procedure. Standardized criteria will be necessary, particularly uniform methods for staging pleural disease and defining the optimal degree of surgical resection extension. Multicenter prospective trials are required to compare various pharmacologic regimens according to the pleural tumor type.

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