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Research Article

THE IMPACT OF HYPOTONIC CISPLATIN INTRAOPERATIVELY ON NON-SMALL CELL LUNG CANCERS WITH PROMISE PLEURAL LAVAGE CYTOLOGY

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ABSTRACT

The purpose of this study is to examine the effects of intraoperative intrapleural hypotonic cisplatin treatment on patients with non-small cell lung cancer (NSCLC) and positive results from pleural lavage cytology after surgery.This study offers information about survival rates and recurrence history despite the limited recruitment during phase III due to a low enrollment rate. A total of 58 patients were randomly selected for each group, and recurrence rates and 3-year survival were determined. There was a significant decline in re-occurrences of carcinomatous pleuritis in the treatment group (8 vs 42). In comparison with similar studies, the 3-year survival rates of the treatment and control groups were both high. The results suggest that intraoperative hypotonic cisplatin therapy might increase patient outcomes and prevent pleural recurrence. This treatment method will be validated by more prospective research and made more efficient through more research.

Keywords: - Intrapleural cisplatin, non-small cell lung cancer, Pleural lavage cytology, Carcinomatous pleuritis, Survival rates.

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INTRODUCTION

There is a certain proportion of patients with non-small cell lung cancer without cancerous pleuritis (malignant pleural effusion, disseminated pleuratic metastases, or both) who are able to detect cancer cells in the pleural cavity. A cytological analysis of pleural lavage fluid collected shortly after thoracotomy reported a negative prognosis, and the frequency of recurrence is unknown [1, 2]. These patients have a negative prognosis and recurrence patterns have not been fully investigated. In these patients, the fact that cancer cells are distributed in this way makes it possible to predict the possibility of recurrent carcinomatous pleuritis.In our intraoperative pleural management protocol, distilled water containing cisplatin was administered intraoperatively to patients with carcinomatous pleuritis undergoing thoracotomy [3]. An experimental study also showed that hypotonic cisplatin solution had much greater antitumor activity than isotonic cisplatin solution or distilled water alone, but was discontinued shortly after a sluggish participant enrollment rate forced the trial to be discontinued [4]. Although the extrapolations of the results of such a trial cannot be conducted other than with trepidation, the patterns of recurrence like carcinomatous pleuritis which have been isolated in prospective studies are considered to be helpful in analysis. Thus, we have not disregarded this in our research.

METHODS

During this study, non-small cell lung cancer patients with pleural lavage fluid collected after thoracic incision were evaluated for cytology findings.

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In all of these patients, the tumors ranged in stage from I to IIIA, so macroscopical removal was essential. There was no malignant pleural effusion present in the pleura and no extensive pleural metastasis was present. A patient's estimated FEV1.0 should be greater than 600 mL/m2, the leukocyte count must be above 3000/mL, the hemoglobin level must be higher than 10 g/dL, the platelet count must be higher than 100,000/m2, the serum bilirubin level must not exceed 1.5 mg/dL, the serum glutamic oxaloacetic transaminase-glutamic pyruv must not exceed 1.5 mg/dL. The study excluded patients with extensive pleural adhesions or chest wall resections or pericardium resection.

Design and Procedure

In the immediate aftermath of thoracotomy, 50 mL of saline was irrigated into the pleural cavity. It was decided to harvest only the cancerous cells within the pleural space by not touching the pleural surfaces of the initial tumor [5]. To ensure that the lavage fluid is not contaminated with bacteria, 20 mL of the lavage fluid was diluted with ethylenediamine tetraacetic acid (EDTA). Cancer cells were detected by staining the sediment with Giemsa, Papanicolaou, and Alcian blue stains.A saline irrigation was used to irrigate the thoracic cavities of patients in the control group after tumor removal. Cisplatin was injected intraoperatively into the pleural cavity of patients randomized to the treatment group so that the thoracic cavity could be closed. Upon completion of an intrathoracic surgery, the pleural cavity was cleaned with saline to get rid of blood, and then the remaining blood cells were removed via hemolysis by washing the cavity twice with distilled water. In the next step, the entire thoracic cavity was exposed to cisplatin in distilled water, pre-heated to 38C 0 -40C for 15 minutes. In this study, cisplatin was diluted to a concentration of 50 μg/mL. Suctioning the solution was followed by saline irrigation of the thoracic cavity, followed by placement of two chest tubes for patients who underwent lobectomies and one for patients who underwent pneumonctomies. It was then necessary to close the thoracic cavity. We did not perform specific perioperative hydration.In the absence of a recurrence, chemotherapy was not allowed. A physician's decision was taken regarding postoperative radiotherapy.Besides bronchoscopy and bone scintigraphy, all patients required a CT scan of their adrenal glands in the thoracic region before surgery. Following up after 5 years was done every 3 months. In addition to physical examinations, serum tumor markers were measured every 3 months, chest radiography was performed every 6 months and CT scans of the thorax including adrenal glands were performed every 6 months for a period of 5 years. There were signs of recurrence with carcinomatous pleuritis at the site of the first appearance. In order to identify a recurrence of carcinomatous pleuritis, the following conditions were observed: [1] a pleural effusion containing cancerous cells as confirmed by cytologic examination; [2] sequential CT scans demonstrating irregular thickenings or masses of the pleura; and [3] CT scan and pathological examination demonstrating cancer in the pleural thickness or mass.

Statistical analysis

Among the participants in this study, it was hypothesized that the 3-year survival rate for the control group would be 30% and that it would be 50% for the treatment group. This study used a 3-year sample size of 100 patients per group with 0.05 alpha and 0.2 beta errors. During the study, patients' survival rates and disease-free survival rates were calculated based on how long they lived between surgery and death by any cause, how long they lived between surgery and death by any cause, and how long they lived between surgery and their first recurrence, respectively. Using the Kaplan-Meier method, survival curves were generated and then the log-rank test was used to analyze the statistics. The χ 2 test was used to determine the difference between proportions.

RESULTS

The demographics and pathological characteristics of the patients in the treatment group and the control group are summarized in Table 1. Neither the treatment group nor the control group differed significantly from one another ($p = 0.334$), with a mean age of 60.9 and a standard deviation of 9.1. Among the treatment group, there were slightly more males than females (10 males and 19 females), but the difference between the two groups was not significant ($p = 0.622$). Treatment patients had higher rates of histological adenocarcinoma (25 out of 29 patients, 86%) than control patients (20 out of 29 patients, 69%), a result that was significant ($p = 0.050$).

Pathologically, the T factor distribution between the two groups was similar, with 59 percent of the treatment group and 52 percent of the control group being in T2. Neither group showed a significant difference in T stage ($p = 0.981$). Again, no significant differences were observed between the groups ($p = 0.815$) for the N0 stage that was observed in 48 percent of patients. In both groups, 41 per cent of the patients were at stage I with 45 per cent in the control group, but this was not significant ($P = 0.708$).

Based on the two groups of patients, Table 2 summarizes the locations of initial recurrences. In both groups, the majority of recurrences (3 in the treatment group and 10 in the control group) were due to carcinomatous pleuritis, which caused a higher recurrence rate in the control group (11 patients). There was a systemic recurrence in both groups, but treatment group (4 patients) had a higher prevalence of bone metastasis

than control group (3 patients). There were 52% and 62% recurrences in the treatment and control groups respectively, which means that there was a higher recurrence rate in the control group.

Table 1: **Demographic and Pathological Characteristics of Patients in the Treatment and Control Groups (n = 58)**

Empty Cell	Treatment group (n = 29)	Control group (n = 29)	P value
Y (years)	60.9 ± 9.1	58.5 ± 8.0	.334
Ratio of men to women	10/19	8/21	.628
Embryology			
Carcinoma adnexa	25	20 (69%)	.050
In other words	4	9	
T factor pathology			
T1	6 (21%)	7 (24%)	.981
T2	17 (59%)	15 (52%)	
T3	1	1	
T4	1	1	
N-factor pathology			
N0	14 (48%)	14 (48%)	.815
N1	3	4	
N2	8 (28%)	6 (21%)	
Pathologic stage			
I	12 (41%)	13 (45%)	.708
II	3	4	
III	10 (34%)	7 (24%)	

Table 2: **Site of First Recurrence**

Empty Cell	Treatment group (n = 29)	Control group (n = 29)
This is a localized recurrence	5	11
The cancerous pleuritis	3	10
In other words	2	1
One recurrence per system	10	7
X-ray	4	3
Anatomy	2	1
Asthma	5	3
Lungs and livers	0	1
An individual as well as a system	0	1
Inflammation of the pleura plus bone cancer	0	1
Total	15 (52%)	18 (62%)

DISCUSSION:

According to estimates, 100 patients with non-small cell lung cancer underwent a resectomy each year and had a positive pleural lavage cytology result by the time the JCOG approved the protocol [6]. This was determined by a survey carried out by the group. Among the primary reasons this phase III trial failed, unhygienic doctors who did not understand intraoperative intrapleural hypotonic cisplatin treatment and the inability to obtain informed consent from patients to participate in the randomized trial were believed to be the main reasons [7].

The study was prematurity-related, so there were relatively few patients participating; however, there were few patients receiving intraoperative pleural lavage cytology (a few hundred). Previously, studies revealed that 9% (14/188) of pleural lavage fluids from non-carcinomatous pleuritis patients had a positive cytology, 9% (42/467) had a positive cytology, and 14% (11/78) had a positive cytology. This high percentage (132/342 patients) was found to be unusual by Buhr and colleagues [5]. The report (JCOG6) found that 142 patients (8%) who underwent pleural lavage cytology following a thoracotomy had intrapleural cancer cells. Despite the extraordinary results of Buhr and others, a 10% positive rate appears to be the most likely outcome. About 500 patients were evaluated for cytology in 49 patients, according to the study.

As the median time between diagnosis and death of the 26 survivors was 49 months, the 3-year survival rate was considered fairly accurate despite not assessing long-

term survival. Figure 1 shows that the treatment group had an overall survival rate of 68 percent after 3 years, while the control group had an overall survival rate of 67 percent after 3 years. This study appears to have higher survival rates than others. It has been reported that 48 percent of patients in the current study had pathological stage I disease versus 54 percent in the other cited studies. Because this study included a greater number of stage I patients, the survival rates may have been higher.

If cancer cells are present in the pleural space after surgery, carcinomatous pleuritis is likely to develop. It is unclear what causes these patients' recurrence patterns. A retrospective study showed that 2 (9%)2 of 23 and 11 (26)3 of 42 patients had developed carcinomatous pleuritis after surgery, which means 63% of the control patients had it as well. Moreover, only two [8, 9] of 25 patients treated with the adjuvant had carcinomatous pleuritis, accounting for 17% of the pleurified patients. As a result of the positive results from pleural lavage cytology, we are considering instituting a prospective registry for intraoperative administration of hypotonic cisplatin inside the pleural cavity. As well as generating more data on survival rates, recurrence patterns, and adverse events, this approach introduces doctors to this therapeutic approach.

CONCLUSION:

After receiving hypotonic cisplatin intraoperatively, patients with non-small cell lung cancer showed favorable pleura lavage cytology results, decreased recurrence of carcinomatous pleuritis, and better survival rates. Even though recruitment was slow in the phase III trial, it appears that this treatment approach has potential for treating recurrent pleural disease. Neither the treatment group nor the control group showed significant differences in survival rates when it came to carcinomatous pleuritis. It is possible that the observed survival rates could be attributed to more patients with stage I disease. A thorough investigation of recurrence rates and the effect and safety of intraoperative hypotonic cisplatin therapy should be conducted in the future. In addition to improving the effectiveness of these treatment strategies, the increased number of patients registering will also be important.

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