Efficacy of adjuvant chemotherapy for lung adenocarcinoma patients with positive pleural lavage cytology findings

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Abstract

OBJECTIVES: Positive pleural lavage cytology (PLC) findings are considered to be predictive of a poor prognosis in patients with non-small-cell lung cancer (NSCLC). We investigated the clinical benefit of adjuvant chemotherapy for lung adenocarcinoma patients with positive PLC findings.

METHODS: We retrospectively reviewed the medical records of lung adenocarcinoma patients who underwent tumor resection and had positive PLC findings between January 2000 and December 2009.

RESULTS: Fifty-three patients (4.8%) of 1114 patients with lung adenocarcinoma had positive PLC findings. The median follow-up period was 33.6 months. Adjuvant chemotherapy was administered to 24 patients (adjuvant chemotherapy group); 7, 8 and 9 patients had pathological Stage I, II and III, respectively. The surgery-alone group comprised 29 patients; 12, 8 and 9 patients had pathological Stage I, II and III, respectively. The 5-year recurrence-free survival (RFS) rates were 34.6 and 15.7% (P = 0.01) in adjuvant chemotherapy and surgery-alone groups, respectively. The rate of distant recurrence was significantly reduced in the adjuvant chemotherapy group (25.0 and 58.6%; P = 0.01). Even for Stage I cases, adjuvant chemotherapy tended to improve the 5-year RFS rate compared with surgery alone (60.1 and 29%; P = 0.11). Multivariate analysis for RFS revealed that adjuvant chemotherapy [hazard ratio (HR), 0.45; P = 0.03], tumour size >30 mm (HR, 2.23; P = 0.02) and lymph node metastasis (HR, 2.67; P < 0.01) were significant independent prognostic factors for recurrence.

CONCLUSIONS: Adjuvant chemotherapy for lung adenocarcinoma patients with positive PLC findings significantly improved recurrence-free survival.

Keywords: Pleural lavage cytology • Adjuvant chemotherapy • Lung cancer • Surgery

INTRODUCTION

Pleural lavage cytology (PLC) findings have been reported to be a prognostic factor in patients with non-small-cell lung cancer (NSCLC), with positive findings predicting a poor prognosis. Despite this, PLC is not included in the current tumour–node–metastasis (TNM) staging system of the World Health Organization (WHO) classification for lung cancer [1]. Positive PLC findings without effusion are the result of cellular exfoliation from tumours at the pleural surface, which represents localized disease, implying an aggressive tumour biology [2]. The frequency of positive PLC findings can vary according to the amount of lavage solution used and timing of the procedure, but previous studies suggest that approximately 4–41% of patients with NSCLC who underwent lung tumour resection had positive PLC findings [2–13]. Many studies have indicated that patients with positive PLC findings have a poor prognosis even if tumours are completely resected in the early stages of lung cancer [2–15].

The Lung Adjuvant Cisplatin Evaluation Collaborative Group performed a large-scale meta-analysis indicating that adjuvant cisplatin chemotherapy improved both overall survival (OS) (5.4% absolute benefit at 5 years) and recurrence-free survival (RFS) (5.8% benefit at 5 years) in patients with NSCLC [16]. Adjuvant chemotherapy is usually reserved for patients with pathologically advanced disease or those who are at high risk for recurrence after surgery [17]. Despite the implications of positive PLC findings in patients with NSCLC, there have been no investigations of the clinical benefit of adjuvant chemotherapy in improving patient survival. Therefore, in this study, we retrospectively reviewed the medical records and evaluated the clinical benefits of adjuvant intravenous systemic chemotherapy in patients with lung adenocarcinoma with positive PLC findings.

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MATERIALS AND METHODS

Patient selection

Between January 2000 and December 2009, PLC was performed immediately after thoracotomy in 1114 consecutive patients with lung adenocarcinoma who had no macroscopic pleural effusions, dissemination or diffuse adhesions at the Department of Thoracic Surgery, Hyogo Cancer Center (Akashi, Japan). Contrast-enhanced chest computed tomography (CT) and brain magnetic resonance imaging were performed to evaluate the preoperative staging. After 2004, positron emission tomography (PET)-CT was performed in addition to them. Staging was designated using the TNM classification according to the 7th edition of the American Joint Committee on Cancer Staging Manual and the Revised International System for staging lung cancer.

For PLC, the pleural cavity was washed with 100 ml of physiological saline solution before any further manipulation of the pulmonary parenchyma. The fluid was transferred to a glass bottle containing heparin and was centrifuged at 1500 rpm for 5 min. The precipitate was stained using the Papanicolaou method, and the specimens were evaluated and classified into five categories (Class I–V). Specimens in Class I–III were categorized as negative, whereas those in Class IV or V were designated as positive. Among 1114 lung adenocarcinoma patients, 53 patients (4.8%) had positive PLC findings and 1061 patients (95.2%) had negative findings.

For adjuvant chemotherapy, patients with a performance status (PS) of 2–4 and those with serious renal or liver function disorders were excluded. Patients selected the therapeutic strategy after receiving a thorough explanation of how the PLC findings determined prognosis and after being informed of the benefits and risks associated with adjuvant chemotherapy.

The institutional review board approved the database used in this retrospective analysis, and written informed consent was obtained from all patients.

Patient follow-up

As described in ref. [18], all patients were evaluated postoperatively at 3-month intervals for 2 years, at 6-month intervals for the subsequent 3 years and once yearly thereafter. Follow-up examinations included chest radiography, CT and haematological and biochemical analyses including tumour markers. PET-CT was not performed in follow-up examinations.

End-points and statistical analyses

As described already in ref. [18], the primary end-points of this retrospective study were OS and RFS. Local recurrence was defined as any recurrence within the same lung, ipsilateral lymph nodes or pulmonary hilum. Distant recurrence was defined as any recurrence other than local recurrence. Statistical analyses were performed using JMP 9 software (SAS Institute, Cary, NC, USA). Student’s t-test and a χ² test were performed to assess the significance of the differences in age, sex, PS, preoperative respiratory function [forced expiratory volume in 1 s (%FEV₁₋₀)], surgical procedure, pathological stage (p-stage), tumour size, preoperative carcinoembryonic antigen (CEA) level, pleural invasion, vascular invasion and lymphatic permeation between the 2 patient groups.

Survival was calculated according to the Kaplan–Meier method, and differences in the distributions were evaluated using the log-rank test. The Cox proportional hazards model, with calculation of the hazard ratio (HR) and 95% confidence interval (CI), was used to evaluate the associations between prognostic factors and RFS rate after pulmonary resection. The threshold for statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

The patients’ clinicopathological characteristics are summarized in Table 1. Fifty-three (4.8%) of 1114 patients with lung adenocarcinoma had positive PLC findings, including 31 male and 22 female patients, with a mean age of 66.6 years. All patients had a PS of 0 or 1. Adjuvant chemotherapy was administered intravenously to 24 patients (adjuvant chemotherapy group). The remaining 29 patients were classified as the surgery-alone group, including 7 patients who...
took uracil-tegafur orally. The patients who underwent adjuvant chemotherapy were significantly younger than those who underwent surgery alone \(P < 0.05\). Preoperative respiratory function \(\% \text{FEV}_1.0\) was evaluated in 17 patients in the adjuvant chemotherapy group and in 21 patients in the surgery-alone group; there was no significant difference in respiratory function between these two groups. There were also no significant differences in sex, PS, surgical procedures, pathological stage, tumour size, preoperative CEA level, pleural invasion, vascular invasion or lymphatic permeation between these two groups. The chemotherapy regimens applied to patients in the adjuvant chemotherapy group are given in Table 2. The median follow-up period was 33.6 months (adjuvant chemotherapy group: 35.5 months, surgery-alone group: 32.5 months).

**Recurrence-free survival**

The 5-year RFS rate was 24.9%. There was no significant difference in RFS according to pathological stage \(P = 0.10\), Fig. 1). Even in Stage I cases, recurrence often occurred 2 years after surgery. The 5-year RFS rates were 34.6 and 15.7\% \(P < 0.01\) for the adjuvant chemotherapy and surgery-alone groups, respectively (Fig. 2). In Stage II and III cases, significantly higher 5-year RFS rates were observed in the adjuvant chemotherapy than in the surgery-alone group (20.2 and 5.8\%, respectively, \(P < 0.01\); Fig. 3A). Furthermore, in Stage I cases, there was a tendency towards a higher 5-year RFS rate in the adjuvant chemotherapy group compared with the surgery-alone group (60.1 and 29\%, respectively; \(P = 0.11\); Fig. 3B).

**Factors related to recurrence-free survival**

Table 3 shows the univariate and multivariate analyses for RFS. Univariate analysis was performed using 11 clinical parameters [age, sex, respiratory function, adjuvant chemotherapy, surgical procedure, tumour size (≥30 mm), lymph node metastasis, preoperative CEA level, pleural invasion, vascular invasion and lymphatic permeation]. Parameters with \(P\)-value <0.20 were included in the multivariate model. Multivariate analysis revealed that adjuvant chemotherapy (HR, 0.45; \(P = 0.03\)), tumour size >30 mm (HR, 2.23; \(P = 0.02\)) and lymph node metastasis (HR, 2.67; \(P < 0.01\)) were significant independent prognostic factors for recurrence. The initial recurrence sites are listed in Table 4. There was no difference in the rate of local recurrence between the adjuvant chemotherapy and surgery-alone groups \(P = 0.65\), whereas the rate of distant recurrence was remarkably reduced in the adjuvant chemotherapy group compared with the surgery-alone group \(P = 0.01\).

**DISCUSSION**

The present study demonstrated the clinical benefit of adjuvant chemotherapy in terms of RFS in patients with lung adenocarcinoma with positive PLC findings. The recurrence rate of the adjuvant chemotherapy group was significantly lower than that of the surgery-alone group. This fact was confirmed in the multivariate analysis, where, in addition to tumour size and lymph node metastasis, adjuvant chemotherapy was identified as an independent prognostic factor for recurrence. Moreover, the rate of distant recurrence was significantly reduced in the adjuvant chemotherapy group.

Several studies have suggested that positive PLC findings obtained during surgery are important prognostic indicators [2–12, 14, 15]. A previous meta-analysis of eight studies demonstrated an association of positive PLC findings with overall, pleural and distant recurrence [ORs of 4.82 (95% CI 2.45–9.51), 9.89 (95% CI 5.95–16.44) and 3.18 (95% CI 1.56–6.46), respectively] [5]. These

<p>| Table 2: Regimens of intravenous adjuvant chemotherapy ((n = 24)) |</p>
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDP + GEM</td>
<td>8</td>
</tr>
<tr>
<td>CBDCA + PTX</td>
<td>7</td>
</tr>
<tr>
<td>GEM</td>
<td>7</td>
</tr>
<tr>
<td>CDDP + TS-1</td>
<td>1</td>
</tr>
<tr>
<td>CBDCA + VP16</td>
<td>1</td>
</tr>
</tbody>
</table>

CDDP: cisplatin; GEM: gemcitabine; CBDCA: carboplatin; PTX: paclitaxel; TS-1: tegafur; VP16: etoposid.
results show that positive PLC findings increase not only the rate of pleural recurrence but also the rate of distant recurrence. Several authors have argued that distant recurrence is often a major pattern of tumour recurrence among patients with positive PLC findings [2, 5, 8, 14]. These facts may imply that surgery alone is not sufficient for this high-risk group of patients and that adjuvant chemotherapy should be considered in order to prevent distant recurrence.

Previous studies have reported that cisplatin-based adjuvant chemotherapy significantly improves survival in patients with NSCLC [16, 19, 20]. These data also show that the clinical benefit of cisplatin-based adjuvant chemotherapy increases as the pathological stage advances. Under the current guidelines, adjuvant systemic chemotherapy is usually only considered for patients with pathologically advanced disease or those who are at high risk for postsurgical recurrence [17]. For patients with early-stage NSCLC, uracil-tegafur taken orally was shown to prolong OS [21]. In the current study, 7 patients who refused intravenous systemic chemotherapy opted for uracil-tegafur therapy as an alternative. However, because the aim of the current study was to evaluate whether intravenous systemic chemotherapy provides a benefit for patients with positive PLC findings, patients receiving uracil-tegafur were included in the surgery-alone group. The efficacy of adjuvant chemotherapy for patients with positive PLC findings was higher than that previously reported for patients with NSCLC [16, 19, 20]. There might be some molecular biological factors that increase the efficacy of adjuvant chemotherapy for patients with positive PLC findings, and their association needs to be elucidated in further investigations.

Although the results of this study were remarkable and showed the importance of adjuvant chemotherapy for adenocarcinoma patients with PLC positive findings, this study had certain limitations. Firstly, as this study is a retrospective, non-randomized, small-sized patient population study, it potentially has a strong selection bias. Although the patients who underwent adjuvant chemotherapy were significantly younger than those who underwent surgery alone (P < 0.01), PS, respiratory function and other oncological factors were not significantly different between these two groups. Age is considered to be an important prognostic factor of lung cancer [22], and the difference in age between the two groups might have affected the results of this study. Moreover, some patients, even those with Stage II and III disease (n = 17), did not receive adjuvant chemotherapy.

| Table 3: Univariate and multivariate analysis of recurrence-free survival (Cox proportional hazards model) |
|------------------|------------------|------------------|------------------|
| **Univariate analysis** | **Multivariate analysis** |
| **HR** | **95% CI** | **P-value** | **HR** | **95% CI** | **P-value** |
| Age (years) | 1.04 | 1.00–1.08 | 0.04 | 1.03 | 0.98–1.08 | 0.22 |
| Sex (male) | 0.78 | 0.42–1.51 | 0.45 | Not included in multivariate model |
| Respiratory function (% FEV1 < 80%) | 1.64 | 0.68–3.77 | 0.526 | Not included in multivariate model |
| Adjuvant chemotherapy (performed) | 0.39 | 0.19–0.75 | <0.01 | 0.45 | 0.21–0.95 | 0.03 |
| Surgical procedure (sublobar resection) | 1.33 | 0.56–2.78 | 0.49 | Not included in multivariate model |
| Tumour size (≥30 mm) | 2.78 | 1.43–5.77 | <0.01 | 2.23 | 1.10–5.77 | 0.02 |
| Lymph node metastasis (present) | 1.77 | 0.92–3.46 | 0.09 | 2.67 | 1.32–5.61 | <0.01 |
| Preoperative CEA (≥5 ng/ml) | 1.52 | 0.19–2.91 | 0.52 | Not included in multivariate model |
| Pleural invasion (present) | 0.52 | 0.16–3.29 | 0.42 | Not included in multivariate model |
| Vascular invasion (present) | 2.96 | 1.37–7.36 | <0.01 | 2.16 | 0.92–5.74 | 0.08 |
| Lymphatic permeation (present) | 1.42 | 0.72–3.00 | 0.31 | Not included in multivariate model |

HR: hazard ratio; CI: confidence interval; % FEV1: forced expiratory volume in 1 s; CEA: carcinoembryonic antigen.
chemotherapy, even though all patients who met the criteria selected the therapeutic strategy after receiving a thorough explanation of how the PLC findings determined prognosis and being informed of the benefits and risks associated with adjuvant chemotherapy. This might be because the clinical benefit of adjuvant chemotherapy had not been confirmed yet in the early part of this study. In addition to this, the regimen of adjuvant chemotherapy was not standardized in this study. Taken together, these factors might have affected the results of this study. Secondly, the epidermal growth factor receptor (EGFR) mutation status was not evaluated in this study in spite of growing evidence that the EGFR mutation status is a prognostic factor in lung adenocarcinoma patients [23, 24]. To minimize the influence of the EGFR tyrosine kinase inhibitors after recurrence, we evaluated the efficacy of adjuvant chemotherapy in improving only RFS, not OS. Thirdly, the international multidisciplinary lung adenocarcinoma classification proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society [25] was not applied in this study. Therefore, considering these issues, prospective randomized trials are required to arrive at a definitive conclusion.

In summary, adjuvant chemotherapy is considered to be an independent factor for predicting RFS in this study. This result implies that intravenous adjuvant chemotherapy should be considered for lung adenocarcinoma patients with positive PLC findings. Although there was no significant advantage of adjuvant chemotherapy in pathological Stage I patients, there was a trend of supporting the benefit of adjuvant chemotherapy for patients with Stage I disease. To the best of our knowledge, this is the first report that describes the efficacy of adjuvant chemotherapy in patients with positive PLC findings. Despite an abundance of data demonstrating that positive PLC findings are an unfavourable prognostic indicator, PLC is still not included in the current TNM staging system of the WHO classification for lung cancer. On the basis of this study and previous studies, we believe that PLC status should be incorporated as a pathological staging factor in the WHO classification for lung cancer. To that end, the method of performing PLC should be standardized. Such inclusion and standardization could lead to more efficient selection of patients who would gain the most benefit from personalized postoperative adjuvant chemotherapy.

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**Conflict of interest:** none declared.

**REFERENCES**


eComment. When and why is it reasonable to perform a pleural lavage cytology in non-small-cell lung cancer patients?

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The pattern of failure after surgery in non-small-cell lung cancer (NSCLC) stays as an open forum of discussion in the scientific community. Positive pleural lavage cytology (PLC) findings are associated with increased risk of lung cancer recurrence in patients undergoing surgical resection, according to a recent meta-analysis [1]. In this setting, we have read with extreme interest the recent article by Ogawa and co-workers [2], who have investigated the clinical benefit of adjuvant chemotherapy in a selected cohort of patients (n = 53) with positive PLC findings, undergoing surgery with curative intent for lung adenocarcinoma. When comparing the long-term results between patients treated with surgery and adjuvant chemotherapy (n = 24) and patients treated with surgery alone (n = 29), they observed a significantly difference (P = 0.01) in terms of 5-year recurrence-free survival (RFS) rates. Accordingly, the Authors concluded their analysis suggested a prognostic (protective) role of adjuvant therapy in patients with positive PLC.

As suggested by several guidelines on the strategy of care in NSCLC patients, the administration of platinum-based adjuvant therapy is clearly recommended in pathological Stage II-III (Grade 1A for ESMO [3] and ACCP [4]) and may be considered also in patients with resected Stage IB disease and a primary tumour >4 cm (Grade 2B for ESMO [5]). Therefore in such patients (pStage II-III and selected cases of pStage IB), PLC findings represent a further negative prognostic factor that would probably influence the long-term outcome in such patients but not the strategy of care, considering that the adjuvant therapy is already recommended (as reported above). In the manuscript of Ogawa and co-workers [2], a total of 26 patients (about 50% of the sample) with positive PLC had Stage II-III disease, of whom 13 underwent surgery alone and 11 underwent surgery with adjuvant chemotherapy. Thus, the positive affect of adjuvant therapy on long-term outcome in these cases may be independent of PLC findings, as reported in the guidelines cited above. Indeed, the same Authors have performed a deeper survival analysis, observing that adjuvant chemotherapy tended to improve the 5-year RFS rate compared with surgery alone (60.1 and 29%; P = 0.11) even when considering Stage-I NSCLC cases only.

On the one hand, we completely agree with the conclusion of the Authors [2], who suggest that adjuvant chemotherapy may be efficacious in patients with positive PLC findings and, accordingly, this factor (PLC) should deserve more consideration in the forthcoming staging classification systems. On the other hand, we suggest that a PLC should only be performed in patients with clinical Stage I where a positive PLC finding stays the main discriminating factor in the planning of the adjuvant therapy. Finally, a randomized clinical trial would definitely clarify the efficacy of adjuvant therapy in these selected cases. We would greatly appreciate the Authors reflections and reactions of the points raised.

Conflict of interest: none declared.

References


