Preoperative chemotherapy increases cytokine production after lung cancer surgery

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Abstract

Objective: Many phase II trials have shown that preoperative chemotherapy for lung cancer is feasible but associated with postoperative morbidity and mortality. However, little is known about the effect of preoperative chemotherapy on surgical stress and postoperative complications associated with surgical intervention. We evaluated the effect of preoperative chemotherapy on perioperative inflammatory cytokine production as a surgical stress marker.

Methods: The study group comprised 38 patients undergoing anatomical lung resection and mediastinal nodal dissection for clinical stage IB/II non-small cell lung cancer during the period October 2001–December 2003. Nineteen patients received a single cycle of cisplatin (80 mg/m²) and docetaxel (60 mg/m²) chemotherapy prior to surgery (neoadjuvant group), and 19 patients underwent surgery without any previous chemotherapy (control group). White blood cell and neutrophil counts and serum concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and granulocyte colony-stimulating factor (GCSF) were determined before surgery and on postoperative days 1 and 3. Postoperative complications were reviewed. Differences were assessed by repeated analysis of variance.

Results: Serum concentrations of IL-6 and GCSF rose significantly on postoperative days 1 and 3 in the neoadjuvant group in comparison to concentrations in the control group, but white blood cell count, neutrophil count, and CRP did not differ between the groups. No major complication occurred in either group.

Conclusions: A single cycle of cisplatin and docetaxel chemotherapy followed by surgery can exacerbate overproduction of inflammatory cytokines during the perioperative period in lung cancer patients.

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Keywords: Lung cancer; Pulmonary resection; Preoperative chemotherapy; Surgical stress; Postsurgical morbidity; Inflammatory cytokine; Interleukin-6

1. Introduction

Radical surgical resection is considered appropriate treatment to provide a survival benefit for patients with early non-small cell lung cancer (NSCLC), especially those without lymph node involvement [1]. Nevertheless, long-term survival is not satisfactory, and the recurrence rate is quite high even after radical surgery, except in patients with stage IA cancer. This is probably due to micrometastasis present at the time of the initial surgery but not detectable by conventional diagnostic methods and therefore not eradicated by surgery [1–3]. Recent studies have shown that preoperative chemotherapy could be effective with complete resection of stage IB/II cancers [4–10].

Preoperative chemotherapy is reportedly associated with increased surgical morbidity and mortality because it induces both a transient and a relatively permanent immune deficit in treated patients [11,12]. However, in another study, no significant differences in mortality, pulmonary morbidity, or complications were noted between surgery patients with and without preoperative chemotherapy [13]. There is still no conclusive evidence that preoperative chemotherapy is associated with increased postsurgical morbidity and mortality. Among the human body responses to surgery, the serum interleukin-6 (IL-6) level is reported to be a sensitive indicator of the degree of surgical stress [14–16]. Furthermore, it has been reported that postoperative IL-6 levels correlate with postoperative complications and mortality [17].

The goal of this study was to evaluate the effect of preoperative chemotherapy on production of selected acute-phase reactants during the perioperative period in patients with localized early-NSCLC.
2. Patients and methods

2.1. Eligibility criteria

Study patients were prospectively selected from among 56 consecutive patients undergoing scheduled pulmonary resection for clinical stage IB (T2N0) or II (T1-2N1, T3N0) histologically proven NSCLC at our hospital during the period October 2001–December 2003. Informed consent was obtained from all patients. Inclusion criteria included age equal to or less than 75 years, performance status of 0 on the Zubrod scale, and no prior cancer treatment. Patients underwent a preinclusion examination consisting of chest X-ray, chest computed tomography (CT), fiberoptic bronchoscopy, abdominal CT, brain CT, or magnetic resonance imaging study. A hilar or mediastinal node with a short-axis diameter of 1 cm or more on a CT scan was considered to be involved with the disease. Mediastinoscopy was not used. Exclusion criteria were the presence of inflammatory findings before treatment including a white blood cell count greater than $10^9$/l, neutrophil count greater than 6.6$\times$10^9/l or C-reactive protein (CRP) value greater than 1.5 mg/dl; inability to undergo chemotherapy because of preexisting conditions such as cardiovascular disease, renal insufficiency, abnormal coagulation study findings.

2.2. Treatment

Patients were randomly assigned to receive preoperative chemotherapy (neoadjuvant group) or to receive no preoperative treatment (control group). Chemotherapy consisted of cisplatin at 80 mg/m^2 and docetaxel at 60 mg/m^2 administered intravenously on the first study day. Care was taken to maintain sufficient hydration on the first chemotherapy day in all patients in the neoadjuvant group. Surgery was scheduled to occur 28 days after chemotherapy.

2.3. Measurement of inflammatory mediators

Peripheral blood samples were taken from each patient’s radial artery at the beginning of anesthesia and 18 h (postoperative day 1) and 66 h (postoperative day 3) after surgery. Each blood sample was divided into two portions: one for the complete blood count analysis and the other for cytokine analysis. Blood was centrifuged at 3000$\times$g. The serum was collected and divided into two portions; one was used for CRP analysis, and the other was stored at $-10^\circ$C for cytokine analysis. Serum IL-6 and granulocyte colony-stimulating factor (GCSF) were assayed in duplicate with commercial enzyme-linked immunoassay kits (IL-6: Fujirebio Co., Tokyo, Japan; G-CSF: Kainos Lab., Inc., Tokyo, Japan).

2.4. Postoperative care

Prophylactic cefmetazole sodium at 2 g per day was injected for 3 days after surgery in both groups. When systemic inflammatory response syndrome (SIRS), as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [18], occurred after the fourth postoperative day, carbapenem antibiotics were intravenously administered. No patient in either group underwent steroid treatment. Non-steroidal anti-inflammatory drugs were given to all patients to treat postoperative wound pain. The chest tube was routinely removed when neither pneumothorax nor chylothorax occurred and the daily amount of chest tube drainage decreased to less than 200 ml.

2.5. Postsurgical morbidity and mortality

The incidence of complications was analyzed to determine whether it was affected by preoperative chemotherapy. Major complications were defined as those requiring intubation, cardioversion, emergency surgery, or transfer to an intensive care unit (e.g. bronchopleural fistula, sepsis, and massive pleural bleeding). Minor complications were defined as wound healing complications; those requiring prolonged chest tube drainage due to pneumothorax, pleuritis, or chylothorax after the seventh postoperative day; or those requiring prolonged intravenous antibiotic administration due to SIRS after the fourth postoperative day.

2.6. Statistical analysis

Fisher’s exact test was used to analyze between-group differences in categorical variables. Student’s t-test was used to assess between-group differences in continuous variables. A P-value of 0.05 or less was considered significant.

The white blood cell and neutrophil counts, CRP, and cytokine levels (mean$\pm$SEM) at each time point were calculated for each group, and repeated measures analysis (ANOVA) with Bonferroni/Dunn correction for multiple comparisons was used to analyze between-group differences at each time point. Differences were considered significant if the P-value was less than 0.05.

3. Results

Forty-two patients were selected for inclusion. Twenty-two patients received preoperative chemotherapy, and 20 patients underwent surgery without prior treatment. Three patients who received chemotherapy were excluded from the study because incomplete resection was performed due to pleural dissemination (2 patients) or vertebral invasion (1 patient). One patient without preoperative chemotherapy was excluded from the study because the pathological findings of the resected specimen indicated small cell carcinoma. As a result, 19 patients in each group were enrolled in this study. There were no significant
3.1. Preoperative chemotherapy

No severe World Health Organization grade III or greater toxicity [19] other than neutropenia occurred after chemotherapy in the neoadjuvant group. Human recombinant GCSF was injected in 5 patients due to neutropenia of less than $0.5 \times 10^9/l$ after the chemotherapy. Neutrophil counts were restored to the normal value within 3 weeks after chemotherapy in all patients.

3.2. Postoperative complications

No major complication occurred in either group. Prolonged chest tube drainage due to pleuritis occurred in 1 patient in the neoadjuvant group.

3.3. Perioperative changes in inflammatory mediators

Postoperative increases in white blood cell and neutrophil counts were observed in both groups, reaching maximum values on postoperative day 1. The white blood cell and neutrophil counts did not differ significantly between the groups (Fig. 1).

Increases in serum CRP, IL-6, and GCSF concentrations were observed in both groups. The CRP value peaked on postoperative day 3 in the neoadjuvant group. The IL-6 and GCSF values peaked on postoperative day 1 in both groups. In response to surgery, peak IL-6 and GCSF concentrations were significantly higher in the neoadjuvant group than in the control group (Fig. 2).

### Table 1

Patient characteristics and surgical information

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant group ($n=19$)</th>
<th>Control group ($n=19$)</th>
</tr>
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<tbody>
<tr>
<td>Median age, years (range)$^a$</td>
<td>63 (42–75)</td>
<td>64 (36–75)</td>
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<tr>
<td>Sex ratio (M/F)</td>
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<td>11/8</td>
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<tr>
<td>Vital capacity (ml)$^b$</td>
<td>3389 (560)</td>
<td>3374 (1198)</td>
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<tr>
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<td>2440 (642)</td>
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<tr>
<td>Extensive</td>
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<tr>
<td>Operation time (min)</td>
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<tr>
<td>Operative blood loss (ml)</td>
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Number of patients is shown unless otherwise indicated. FEV1.0, forced expiratory volume in 1 s; standard, ipsilateral mediastinal dissection; extensive, bilateral mediastinal dissection; n.s., between-group difference not significant by Fisher’s exact test (categorical variables) and by Student’s $t$-test (continuous variables).

$^a$ Range.

$^b$ Mean (SD).
4. Discussion

Stage I/II NSCLC is best treated by surgical resection, but long-term survival remains poor even with early diagnosis. The 5-year survival rate with complete surgical resection is approximately 50% in stage IB patients, mainly because of distant metastasis [1]. Some stage IIIA cancers are not detectable by conventional diagnostic methods and therefore not eradicated by surgery. The need for combined-modality treatment in patients with clinical stage IB or II cancer is evident. Use of neoadjuvant chemotherapy for early-stage lung cancer is based on the Goldie and Coldman hypothesis that tumor response increases and the number of chemoresistant cells decreases as tumor size decreases [20]. Potential advantages of neoadjuvant chemotherapy include early control of micrometastases, better tolerability than with postoperative adjuvant therapy, improved resectability rates due to reduction of primary tumor size, and guidelines for postoperative treatment strategies based on pathological assessment of the patient’s response [21].

There is evidence that chemotherapy induces both a transient and a relatively permanent immune deficit in treated patients. Some reports describe increased perioperative complications in patients who underwent chemotherapy prior to lung cancer surgery in comparison to patients who did not [11,12]. In another study, no significant differences in mortality, pulmonary morbidity, complications related to healing, length of stay, or readmission rates were noted [13]. The reason for this discrepancy is that perioperative complications after neoadjuvant chemotherapy are related to multiple factors, including the patient’s performance status and the regimen, intensity, duration, and number of chemotherapy cycles. Therefore, to clarify the effect of preoperative chemotherapy on surgical stress, patients with a good performance status who received a single cycle of preoperative chemotherapy for early-stage NSCLC were enrolled in the present study.

Major surgical intervention impairs the patient’s immune system, causing postoperative complications such as infection and cancer metastasis. Systemic cytokine response induced by surgical damage has been reported and is thought to have an important effect on the immune system. IL-6 and GCSF are major mediators of the acute-phase protein response to tissue damage caused by surgical intervention and chemotherapy [14–16,22].

Many reports confirm our finding that IL-6 concentration in the control group on postoperative day 1 after pulmonary resection ranged from 100 to 150 pg/ml [23–25]. Also on day 1, the neoadjuvant group showed a significant peak in serum IL-6 concentration in comparison to the control group.

Elevated GCSF production is reportedly related to surgical stress [16,26]. This elevation was shown to be much higher in esophagectomy patients than in gastrectomy or cholecystectomy patients. Exacerbated GCSF production may be related to IL-6 production and/or to previous myelosuppression induced by neoadjuvant chemotherapy [22].

Our findings suggest that a single cycle of cisplatin and docetaxel chemotherapy plus surgery can exacerbate overproduction of inflammatory cytokines during the perioperative period in early-stage lung cancer patients, in comparison to that in the patients who undergo
surgery without preoperative chemotherapy. Multi-cycled neoadjuvant chemotherapy for advanced-stage lung cancer patients may have an even greater negative effect on the patient’s postoperative condition.

References