Paclitaxel/Platinum-based Perioperative Chemotherapy and Surgery in Stage IIIA Non-small Cell Lung Cancer

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Objective: The objectives of the present study were to assess the efficacy and tolerability of perioperative paclitaxel/platinum-based chemotherapy and surgery in patients with stage IIIA clinical N2 (cN2) non-small cell lung cancer (NSCLC).

Methods: Clinical N2 was defined as either >15 mm or >10 mm and multiple nodes on computed tomography (CT) scan. Thirty-four chemotherapy-naïve patients with stage IIIA cN2 received preoperative paclitaxel/cisplatin for two cycles and then underwent surgery. The treatment with paclitaxel/carboplatin was repeated for three cycles after the operation.

Results: Of the 34 patients, none achieved a complete response (CR) and 22 achieved a partial response (PR), resulting in a response rate of 65%. Among 29 patients (85%) who had received thoracotomy, 25 (74%) underwent complete resection. Two pathological CRs were observed and mediastinal nodes were free of tumor in 21%. Grade 3–4 toxicity was uncommon and treatment-related mortality was not observed. The median time to progression (TTP) was 12.1 months [95% confidence interval (CI) 8.3–15.9 months] and median overall survival (OS) was 23.6 months (95% CI 17.7–30.2 months).

Conclusions: Paclitaxel/platinum-based perioperative chemotherapy and surgery for patients with stage IIIA cN2 NSCLC is effective and well tolerated.

Key words: neoadjuvant chemotherapy – non-small cell lung cancer – paclitaxel – platinum

INTRODUCTION

At the time of diagnosis, ~20% of patients with newly diagnosed non-small cell lung cancer (NSCLC) exhibit stage IIIA disease with clinical mediastinal lymph node involvement (cN2) (1). The majority of patients with locally advanced stage IIIA NSCLC, particularly those with cN2, eventually develop distant metastases within several months of local treatment. Although the complete resection is technically feasible for patients at stage IIIA cN2, their 5-year survival is only 10%, mainly because of the development of distant metastases (2). This poor outcome has prompted investigations of additional chemotherapy given before or after resection. Regarding neoadjuvant chemotherapy, several phase II trials involving combinations of cisplatin and older drugs have shown that neoadjuvant chemotherapy is feasible in patients with stage IIIA disease (3–5). However, the results of randomized phase III trials of neoadjuvant chemotherapy in stage IIIA disease are inconsistent, because of small sample sizes, short follow-up periods or the use of older drugs (6–9). Recently, the results of several phase II trials on neoadjuvant chemotherapy using newer agents have become available for locally advanced NSCLC (10–15). In the present study, we tested a paclitaxel/cisplatin combination regimen, which has already been well established as a palliative chemotherapy in advanced NSCLC, as a neoadjuvant chemotherapy for stage IIIA NSCLC patients. Two phase III randomized trials have demonstrated the superiority of first-line paclitaxel/cisplatin in stage IIIB/IV NSCLC over older regimens (16,17). Although the role of post-operative chemotherapy has not been clearly defined in the neoadjuvant setting, the majority of medical oncologists recommended additional post-operative chemotherapy for patients experiencing major tumor regression after neoadjuvant chemotherapy. In two neoadjuvant trials by Roth et al. (7) and the Bimodality Lung Oncology Team (BLOT) (12), post-operative chemotherapy was tried for patients who had a major or minor response to pre-operative chemotherapy and whose lesion was resectable. The patients with prior chemotherapy and surgery possibly have poor
performance status and reduced tolerability to post-operative chemotherapy. Therefore, we decided to administer three cycles of paclitaxel/carboplatin post-operatively in our trial, based on the reports that paclitaxel/carboplatin showed response rates and survivals that were comparable with those of combinations of other new platinum-based agents, with more favorable toxicity profiles, better tolerability and compliance in advanced NSCLC (17–19). The primary objective of this trial was to evaluate the effects of a perioperative regimen of paclitaxel/platinum for patients with stage IIIA cN2 NSCLC in terms of response rate, toxicity and the influence on resectability and mediastinal downstaging. The secondary objective was to determine prospectively its effect on patient survival.

PATIENTS AND METHODS

PATIENT ELIGIBILITY

Eligibility requirements for study entry included a diagnosis of stage IIIA NSCLC with cN2 node defined as follows: a lymph node of short axis diameter exceeding 15 mm on computed tomography (CT) scan; cases with a diameter between 10 and 14 mm were included only if there was more than one node; if only a single lymph node of diameter between 10 and 14 mm was present, it was included only after being confirmed by mediastinoscopic biopsy.

Additional eligibility criteria included: age 18–70 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; presence of at least one bidimensionally measurable lesion; predicted 1 s forced expiratory volume (FEV1) >2.01 or post-operative predicted FEV1 >1.0 l; normal cardiac and bone marrow (leukocytes >4.0 × 10^9/l, platelets >100 × 10^9/l); and adequate hepatic and renal function. Patients who had received previous chemotherapy, radiotherapy, or with active infection were excluded from this study. All enrolled patients provided written informed consent, and the institutional review board of Seoul National University Hospital approved the study protocol.

TRIAL DESIGN AND TREATMENT PLAN

Neoadjuvant chemotherapy. Paclitaxel 175 mg/m^2 was administered as a 3 h intravenous (i.v.) infusion after hypersensitivity prophylaxis, which consisted of i.v. dexamethasone 20 mg, diphenhydramine 50 mg, and famotidine 20 mg on day 1. After the paclitaxel infusion, cisplatin 60 mg/m^2 was infused over 30 min after i.v. hydration with 1.5 l of saline and administration of standard antiemetics on day 1. Treatment was repeated on a 21 day treatment cycle for two cycles.

Surgery. After two cycles of chemotherapy, tumor response was assessed by a CT scan of the chest and upper abdomen, and by bronchoscopy if indicated. Those patients who achieved a major objective response or disease stabilization without evidence of progressive disease underwent surgeon’s evaluation for thoracotomy, and standard curative resection was attempted within 3–6 weeks of the second administration of paclitaxel and cisplatin.

At thoracotomy, the extent of the pulmonary resection was left to the discretion of the attending surgeon as long as the resection chosen provided complete removal of the primary lesion with negative gross and microscopic margins (R0). All accessible hilar lymph nodes were dissected from the specimens, and a complete mediastinal lymph node dissection was performed in all patients. Radiotherapy was scheduled for patients with unresectable stable disease or local progressive disease after neoadjuvant chemotherapy.

Post-operative therapy. Patients who underwent complete resection received post-operative paclitaxel/carboplatin chemotherapy, beginning within 8 weeks of thoracotomy. Paclitaxel was given prior to carboplatin at a dose of 135 mg/m^2 as a 3 h i.v. infusion with the same pre-medication as mentioned for neoadjuvant schedule. Carboplatin was administered as a 30 min i.v. infusion. The dose was calculated according to the Calvert formula, with an area under the curve (AUC) of 5 using a calculated glomerular filtration rate from the Cockcroft–Gault formula. Both drugs were given on day 1 of a 21-day treatment cycle for three cycles. Post-operative radiotherapy, starting 4 weeks after surgery, was administered to patients with a positive resection margin [R1 and R2 (micro- and macroscopically incomplete resection, respectively)] with a total standard fractionation dose of 60 Gy. These patients with incomplete resection also received paclitaxel/carboplatin chemotherapy after radiation.

Dose delay and modifications. Each chemotherapy cycle was started only if the ANC and platelet counts on the day of treatment were ≥1.5 × 10^9/l and ≥100 × 10^9/l, respectively. Treatment was delayed until this level was achieved and, if the delay was >2 weeks, the patient was taken off the treatment. Chemotherapy was administered at 75% of the originally planned dose in the event of grade 4 febrile neutropenia, grade 4 thrombocytopenia, thrombocytopenia of any grade accompanied by bleeding or any grade 4 non-hematological toxicity except for alopecia. Both paclitaxel and cisplatin doses were reduced by 25% when grade 2 neurotoxicity occurred, and the administration of these agents was suspended until recovery when the neurotoxicity was worse than grade 2.

PATIENT EVALUATION

A complete history taking, physical examination, complete blood cell count with differential, serum biochemistry, spirometry, bronchoscopy, CT scan of the chest and upper abdomen, and electrocardiography (ECG) were performed at baseline. Patients were monitored by recording their toxic event histories. Complete blood cell counts with differential and serum chemistry determinations were repeated just before the start of each chemotherapy cycle. Response evaluations were performed using the World Health Organization (WHO) criteria (20). Complete response (CR) was defined as the
complete disappearance of all disease on radiographic and physical examination. Partial response (PR) was defined as a >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions. Stable disease (SD) was defined as no detectable change in the tumor volume of all lesions. Progressive disease (PD) was defined as a >25% increase in the sum of the products of the perpendicular diameters of all the measurable lesions or by the appearance of new lesions. All toxicities were coded according to the WHO common toxicity criteria and guidelines (20). After the completion of treatment, regular follow-up visits were made at 3 month intervals for the first 2 years and twice annually thereafter.

**STATISTICAL ANALYSIS**

All patients enrolled were monitored for response, treatment-related toxicity, time to disease progression (TTP) and time to death. Response, TTP and overall survival (OS) were analyzed in all enrolled patients and additional analyses were carried out in tumor resection cases for TTP, OS and resection-related outcomes. Toxicity analyses included all patients who received at least one infusion of paclitaxel and cisplatin. TTP and OS were calculated from the date of treatment and estimated using the Kaplan and Meier method (21). Comparisons between groups were performed using the log-rank test for time to event variables.

**RESULTS**

**PATIENT CHARACTERISTICS**

Thirty-four patients with stage IIIA cN2 NSCLC registered at Seoul National University Hospital between October 2000 and June 2003 were enrolled in this study. The baseline patient characteristics of the 34 patients are listed in Table 1. There were 27 men and seven women, with a median age of 61 years (range 39–69 years). Twenty-one (62%) patients had an ECOG performance status of 1 and squamous cell carcinoma was the predominant histological subtype (40%). Most patients presented with evidence of multiple enlarged mediastinal lymph nodes on chest CT scan. Two patients presented with only one mediastinal lymph node of diameter 10–14 mm, and underwent mediastinoscopy which confirmed tumor involvement.

**RESPONSE TO CHEMOTHERAPY AND ADDITIONAL TREATMENT**

The treatment and outcome of patients are summarized in Fig. 1. The overall clinical response rate (ORR) for all 34 assessable patients was 65% [95% confidence interval (CI), 54–75%]. There was no CR, 22 (65%) PRs, 10 (29%) SDs and two (6%) PDs. Two patients with PD had local PD and received salvage radiotherapy. All responses were confirmed by an independent radiologist at least 3 weeks after the completion of chemotherapy. Based on this restaging, all 22 clinical responders and the 10 patients with SD were evaluated for resection by a team composed of a thoracic surgeon, a medical oncologist and a pulmonologist. One patient with SD was judged to have unresectable disease and, therefore, received radiotherapy, whereas the remaining two patients (one PR and one SD) refused additional treatment. Thus, 29 patients (85%) (21 PRs and eight SDs) underwent thoracotomy: 18 lobectomy, two bilobectomy and nine pneumonectomy. Resections were found to be complete with clear resection margins in 25 cases (74%), and two pathological CRs (7%) were reported. Pathological clearance of the mediastinal lymph nodes in patients with tumor resection was observed in six N0 (21%) and six N1 (21%) patients, but 17 patients remained N2 (58%). Of the 25 complete resection patients, 20 patients received adjuvant chemotherapy and 18 patients finished all three cycles of planned chemotherapy. Five patients did not receive adjuvant chemotherapy: two patients refused, two had post-operative pneumonia and one had a poor PS. Five patients received post-operative radiotherapy. Reasons for receiving radiotherapy included incomplete resection with positive resection margin (n = 4) and medical panel’s decision even with a negative resection margin (n = 1). Of the four incomplete resection patients who received post-operative radiotherapy, three patients did not receive adjuvant chemotherapy (one PD during radiotherapy, one pneumonia during radiotherapy and one patient’s refusal), whereas the other patient completed the scheduled therapy. Therefore, in total, 21 patients received 60 cycles of adjuvant chemotherapy.

**TOXICITY AND DOSE INTENSITY**

All 34 patients completed the two planned pre-operative chemotherapy cycles and were assessed for toxicity as
summarized in Table 2. Grade 3–4 hematological toxicity was uncommon. Grade 3 leukopenia was observed in three cycles and only one had febrile neutropenia. No grade 3–4 anemia or thrombocytopenia were observed. Grade 3–4 non-hematological toxicity was also uncommon apart from alopecia. A grade 1 hypersensitivity reaction occurred in two patients who developed facial flushing and chest tightness during paclitaxel infusion. This was successfully prevented during subsequent cycles by further pre-medication and a 6 h infusion schedule. Grade 1–2 peripheral neuropathy occurred in 21%. No early or toxic deaths occurred. Toxicity was responsible for the dose adjustment of subsequent cycles. The mean dose intensity per administered cycle was 173.7 mg/m²/3 weeks for paclitaxel and 59.5 mg/m²/3 weeks for cisplatin; 99.3% of the planned total dosage was administered. In total, 21 patients received 60 cycles of post-operative chemotherapy. The mean dose intensity per administered cycle was 132.8 mg/m²/3 weeks for paclitaxel and AUC 4.92/3 weeks for carboplatin; 98.3% of the planned total dosage was administered. Toxicities were similar to those of pre-operative chemotherapy and no additional and unexpected toxicities occurred (Table 2). No post-operative deaths with complications starting within 1 month of resection occurred. Post-operative morbidities occurred in two cases, and both were post-operative pneumonia.

Table 2. Toxicity of chemotherapy

<table>
<thead>
<tr>
<th>Toxicity, WHO criteria</th>
<th>Worst grade</th>
<th>Pre-operative chemotherapy (68 cycles)</th>
<th>Post-operative chemotherapy (60 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cycles</td>
<td>%</td>
<td>No. of cycles</td>
</tr>
<tr>
<td>Hematological toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1–2</td>
<td>43</td>
<td>14</td>
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<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>1–2</td>
<td>21</td>
<td>31</td>
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<tr>
<td></td>
<td>3</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Thrombocytopenia</td>
<td>1–2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Non-hematological toxicity</td>
<td></td>
<td></td>
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<tr>
<td>Nausea/vomiting</td>
<td>1–2</td>
<td>30</td>
<td>44</td>
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<tr>
<td></td>
<td>3</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>1–2</td>
<td>14</td>
<td>21</td>
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<td></td>
<td>3</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Myalgia/arthralgia</td>
<td>1–2</td>
<td>12</td>
<td>18</td>
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<td>3</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Alopecia</td>
<td>1–2</td>
<td>35</td>
<td>53</td>
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<td></td>
<td>3</td>
<td>18</td>
<td>26</td>
</tr>
</tbody>
</table>
TTP AND SURVIVAL

At the time of this analysis, after a median follow-up of 24.3 months (range 6.1–47.8 months), 24 patients (75%) experienced recurrence or disease progression, and 17 patients (50%) died. All deaths were related to tumor progression. Locoregional recurrence or progression occurred in eight patients (33%), distant metastases in 13 patients (54%), and three patients developed both locoregional and distant metastases (13%). There were five brain metastases, all of which were the sole site of relapse or progression. The median TTP for all patients \((n = 34)\) was 12.1 months (95% CI 8.3–15.9 months) (Fig. 2). Seventeen patients remain alive (50%), and the Kaplan–Meier estimates of median and 1-year survival for all patients \((n = 34)\) were 23.6 months (95% CI 17.7–30.2 months) and 70%, respectively (Fig. 3). The median TTP was 12.3 months (95% CI 10.0–14.6 months) in 25 complete resection patients, as compared with 8.1 months in patients with incomplete resection or without resection \((P = 0.045)\) (Fig. 4). The median OS was significantly longer in 25 complete resection patients than in patients with incomplete resection or without resection (not yet reached versus 10.4 months, \(P = 0.007\)) (Fig. 5).

DISCUSSION

Although currently many controversial opinions exist regarding the optimal management of locally advanced NSCLC, induction therapy before surgery is considered mandatory for the management of marginally resectable stage IIIA NSCLC (defined by the presence of multilevel or bulky N2 disease). During the last 10–15 years, many phase II and III trials have investigated multimodality treatment strategies that include neoadjuvant chemotherapy and surgical resection in patients with stage III NSCLC. The substantial variability in the design of these trials makes interpretation of the results difficult. However, it is well recognized that patients with stage III NSCLC are consistently more sensitive to pre-operative chemotherapy than patients with stage IV disease (22), and recently several phase II neoadjuvant chemotherapy trials have been conducted using combinations of new platinum-based agents (10–15).

In this study, we decided to test paclitaxel/cisplatin combination regimen as a neoadjuvant chemotherapy in locally advanced NSCLC. The regimen has already been well established and is frequently administered as a palliative chemotherapy in advanced NSCLC. In addition, three cycles of paclitaxel/carboplatin were administered post-operatively. The dose of paclitaxel was attenuated to 135 mg/m², because the patients who had received pre-operative chemotherapy and underwent surgical resection might have a poor performance status and lower tolerability to post-operative chemotherapy. We previously reported the efficacy and tolerability of this modified regimen with attenuated doses of paclitaxel/carboplatin combination in elderly and/or weak patients (23). Our prospective study conducted in 34 patients with stage IIIA cN2 revealed that paclitaxel/cisplatin combination chemotherapy was well tolerated. The majority of patients were able to receive the planned dose. No treatment-related death occurred and only one patient needed hospitalization for febrile neutropenia out of a total of 68 cycles administered to 34 patients. Non-hematological toxicity was also mild. Moreover, the incidences of both perioperative morbidity (7%) and mortality (0%) after neoadjuvant chemotherapy were low. Our results confirm the recent retrospective analysis in 380 NSCLC patients, which found no significant difference in the overall incidence of perioperative morbidity and mortality in patients who received neoadjuvant chemotherapy plus surgery versus surgery alone (24). In the present study, after tumor resection with two cycles of neoadjuvant chemotherapy, patients received three cycles of additional post-operative chemotherapy. Post-operative chemotherapy with paclitaxel/carboplatin
showed excellent tolerability and compliance, and 18 of 20 patients who had received adjuvant chemotherapy finished three planned cycles of chemotherapy. The good tolerability observed in our trial was not offset by a loss of activity; an ORR of 65% and a complete resection rate of 74% were achieved. The median TTP for all patients (n = 34) was 12.1 months (95% CI 8.3–15.9 months) and the median and 1-year survival for all patients (n = 34) were 23.6 months (95% CI 17.7–30.2 months) and 70%, respectively. A considerable median (not yet reached) and 2-year survival (65.8%) was achieved in 25 complete resection patients. In the present study, we adopted lymph node size-based criteria on CT scan for staging the mediastinum.

The sensitivity and specificity of CT scan for detection of metastasis to the lymph nodes has been variable. A meta-analysis which included 20 studies demonstrated that the pooled sensitivity of CT scan was 0.57 (95% CI 0.49–0.66), while the pooled specificity was 0.82 (95% CI 0.77–0.86) (25). The overall positive predictive value and negative predictive value of CT scan for a patient were 0.56 (range 0.26–0.84) and 0.83 (range 0.63–0.93), respectively. This inconsistency has been attributed mainly to the variable correlation of lymph node size with the presence of malignancy. All but three studies involved in this meta-analysis used a >10 mm short axis diameter as the criterion for nodal positivity. However, the probability of mediastinal metastases increased with increasing size of lymph node. Application of a >15 mm short axis diameter as a positive criterion for mediastinal metastasis resulted in an accuracy which ranged the from 74 to 90% (26–27). Staples et al. (28) reported a study of 151 patients, in which the accuracy was 81%, when they used a >15 mm long axis diameter as the criterion for nodal positivity. Previously, we had also reported that the accuracy was 88.8–90.0% in cases of >14–16 mm short axis diameter as a positive criterion for mediastinal metastasis (29).

Mediastinoscopy has long been considered a ‘gold standard’ test for mediastinal staging. However, it has also continued to be the subject of debate. Although some consider the procedure essential in the evaluation of the mediastinum in lung cancer, others view the procedure as overly invasive, with a comparatively high rate of morbidity and occasionally mortality. Therefore, we used CT scan with the aforementioned positive criteria as a mediastinal staging method, avoiding invasive mediastinoscopy. In our results, somewhat disappointingly, perhaps, is the fact that the pathological determination of response showed two CRs (7%), six downstaging to N0 (21%) and six downstaging to N1 (21%) compared with the high degree of activity determined clinically. Significant tumor bulk may have played a role in this outcome, because the majority of our patients had visible stage IIIA disease involving the mediastinum according to the inclusion criteria as mentioned above.

Van Zandwijk et al. (10) reported results of a phase II trial that evaluated the activity of a monthly schedule of gemcitabine/cisplatin as induction chemotherapy for biopsy-proven stage IIIA (N2) NSCLC. A response rate of 72% was obtained, 71% underwent complete tumor resection with one patient achieving pathological CR, while 60% of patients experienced grade 3–4 thrombocytopenia. Median survival of all recruited patients was 18.9 months, with an estimated 1-year survival rate of 69%. In another phase II trial by Migliorino et al. (11), a 3-week schedule of gemcitabine/cisplatin was examined as an induction chemotherapy in 70 patients with stage III NSCLC. Although a reduction in hematological toxicity was observed, grade 3–4 thrombocytopenia remained the main hematological toxicity, and occurred in 26% of patients. The response rate (68%), pathological downstaging rate (19%) and median survival (14.5 months) were similar to those achieved with the monthly schedule. Response rates and complete resection rates of paclitaxel/cisplatin combination in our trial were similar to gemcitabine/cisplatin combination and their toxicity profiles...
were more favorable. Our results are also comparable with those of other phase II trials of taxane/platinum combinations as an induction chemotherapy (12–14). We consider paclitaxel/platinum-based perioperative chemotherapy and surgery very effective, with manageable toxicity, and propose that it be tested further as a treatment for stage IIIA NSCLC.

References