Adjuvant Cisplatin and Docetaxel for Non-small Cell Lung Cancer

The Hospital of the University of Pennsylvania Experience

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Introduction: Cisplatin and docetaxel (Doc) are commonly used for adjuvant therapy for non-small cell lung cancer based on extrapolation from the metastatic setting. Nevertheless, essentially no data have been published on this regimen in the adjuvant context, leading to controversy, particularly surrounding feasibility.

Methods: Using a tumor database augmented with chart reviews, we retrospectively evaluated treatment outcomes of all patients receiving postoperative cisplatin (75 mg/m²) and Doc (75 mg/m²) between August 2003 and November 2008. During this period, this regimen was considered to be the first choice regimen for sufficiently fit patients at the University of Pennsylvania.

Results: The database captured 54 patients. Overall, 85.2% received all four planned cycles (83.3% at full dose). Chart review allowed definitive assessment of toxicity in 47 patients. A single patient (2%) died of grade 5 febrile neutropenia. There was no grade 4 toxicity, and 8.5% experienced grade 3 febrile neutropenia. No febrile neutropenia was observed in 26 patients given prophylactic pegfilgrastim. The incidence was 23.8% in the 21 patients not given pegfilgrastim during the first cycle; 6.4% each experienced grade 3 gastrointestinal, anorexia, nausea, and fatigue, and 2.1% experienced grade 3 diarrhea. Median progression-free survival was 17.9 months, and median overall survival has not been reached.

Conclusion: Cisplatin and Doc are feasible in the adjuvant setting with superior dose delivery and convenience compared with historic data with cisplatin and vinorelbine.

Key Words: Cisplatin, Docetaxel, Adjuvant.

Lung cancer is the leading cause of cancer-related death in the United States. Less than half of patients undergoing definitive surgical resection for early-stage non-small cell lung cancer (NSCLC) are cured of their disease.1,2 Chemotherapy has been used in an attempt to improve outcomes. Treatment with cisplatin-containing doublets resulted in a 5.4% absolute survival benefit at 5 years in the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis.3 Two of the trials included in this meta-analysis, ANITA4 and JBR.10,5 used only cisplatin (CDDP) and vinorelbine (vin); and in the largest trial to date, International Adjuvant Lung Trial (IALT), more than 25% of patients enrolled onto the chemotherapy arm received this regimen. Forest plots in LACE showed a greater survival advantage in these two CDDP-vin containing trials than for any other regimens in the analysis. Further, when subgroups were analyzed in LACE, CDDP-vin adjuvant therapy provided a larger survival advantage compared with other CDDP doublets. Thus, CDDP-vin has set the standard of care for adjuvant therapy and, to date, remains the most widely investigated chemotherapy combination in the modern adjuvant era.

Docetaxel (Doc)-containing regimens were not studied in any of the trials comprising LACE. Nevertheless, the TAX326 study demonstrated trends toward improved response rate (0.029), overall survival (OS, 0.44), and quality of life (p=0.64 for lung cancer symptom scale and p=0.16 for EuroQol) for CDDP-Doc compared with CDDP-vin in the metastatic setting. This trial prompted many thoracic oncologists to hypothesize that the CDDP-Doc doublet might be superior in the adjuvant setting, and this regimen has been included as one of four featured in the ongoing phase III intergroup trial, E1505, comparing cisplatin-based chemotherapy versus chemotherapy plus bevacizumab. Others have argued that extrapolation from the metastatic setting is a flawed assumption and that dose delivery...
of CDDP-Doc is not feasible because of toxicity, particularly myelosuppression, in the postoperative period.

At the Hospital of the University of Pennsylvania, CDDP-Doc was adopted as the standard adjuvant regimen after TAX-326. Therefore, we set out to capture all patients treated at our institution in the adjuvant setting using this regimen.

METHODS

Database

Information was prospectively entered into the password-protected tumor database, which was maintained on Microsoft Access. Data were extracted for all patients treated with curative-intent surgery followed by at least one cycle of CDDP-Doc at the University of Pennsylvania. Data for baseline characteristics, histology, treatment, progression, and survival were all collected prospectively, entered into the database, and extracted from it for this analysis. Toxicity data were obtained retrospectively by chart review and graded by CTCAE version four. When available, social security death index was used to augment survival data in patients lost to follow-up.

Data Extraction

Toxicity data were extracted retrospectively by chart review. To be considered evaluable for toxicity, a complete review of systems with specific commentary on presence or absence of symptoms, and their severity was required. When chart records were ambiguous as to the grade of toxicity, we defaulted to the higher grade.

Treatment data were extracted from order sheets. These sheets were signed by the practitioner and verified by a pharmacist; in addition, it should be noted that two nurses independently signed the orders to confirm that the written therapy was actually administered.

Treatment

Between August 2003 and November 2008, CDDP-Doc was considered the first choice regimen for eligible patients. Patients were treated with CDDP 75 mg/m² and doc 75 mg/m² on day 1 of a 21-day regimen. Patients were given 1 liter of normal saline before and 500 ml after cisplatin; as needed, home intravenous fluid (IVF) was administered. Patients were given individualized antiemetic regimens routinely using 5HT3 inhibitors; aprepitant was used when available. Pegylated filgrastim was used as needed and in some patients, as prophylaxis during the first cycle.

Statistical Analysis

Data queried from Microsoft Access were exported into Microsoft Excel where all calculations were performed. The primary study end point was feasibility, as measured by number of cycles administered. Prespecified secondary end points included toxicity, dose reductions, OS, and median survival. OS and progression-free survival (PFS) were plotted by the standard Kaplan method. Median actual overall and PFS were arithmetically calculated in Microsoft Excel.

RESULTS

Demographic Data

Our tumor database captured 54 patients treated between August 2003 and November 2008 with this regimen after curative-intent surgery. Demographic data are shown in Table 1. Overall, 46.3% of patients were female. African American patients represented 14.8% of the population. One patient had PS2, and another patient had PS3; 18.5% had PS0, and the remaining 77.8% of patients had PS1. 61.1% of patients had stage I or II NSCLC; 25.9% had stage IIIa NSCLC, 11.1% had stage IIIb disease, and a single patient (1.9%) had stage IV NSCLC. All patients with IIIB disease qualified for this designation on the basis of T4 involvement and not N3 disease. One patient had disease invading the main pulmonary vein, and five had satellite nodules; 63% of patients had adenocarcinoma, and 20.4% squamous cell carcinoma.

| Table 1. Baseline Characteristics (n = 54) |
|-----------------|-----------------|
| Median age (range) | 58.5 (34–74) |
| Sex | Male 29 (53.7) Female 25 (46.3) |
| Race | Caucasian 41 (75.9) African American 8 (14.8) Other 6 (9.3) |
| ECOG performance status | 0 10 (18.5) 1 42 (77.8) 2 1 (1.9) 3 1 (1.9) |
| Stage | I 14 (25.9) II 19 (35.2) IIIa 14 (25.9) IIIb 6 (11.1) IV (isolated brain) 1 (1.9) |
| Tumor histology | Adenocarcinoma 34 (63) Squamous cell carcinoma 11 (20.4) Large cell carcinoma 4 (7.4) BAC or adenocarcinoma with BAC features 3 (5.6) NSCLC, NOS 2 (3.7) |
| Smoking status (for 45 patients with data available) | Any history of smoking 35 (79.6) Never smoker 9 (20.4) |
| Surgery type | Lobectomy 42 (77.8) Pneumonectomy 7 (13) Other 5 (9.3) |
| Treated with adjuvant radiation therapy | 9 (16.7) |

Percentages are given in parentheses.

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

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Dose Delivery

Overall, 85.2% of patients received all four planned cycles of CDDP-Doc, 5.6% received 3 cycles, 1.9% received 2 cycles, and 7.4% received one cycle. Two patients required dose reduction, one of whom received all four cycles of therapy. Hence, 83.3% of the overall cohort were treated with four cycles at full dose. Two of the four patients receiving a single cycle of CDDP-doc subsequently received three additional cycles of carboplatin-doc.

The minimum interval from surgery to chemotherapy was 3.7 weeks, the maximum was 21.9 weeks, and the median was 8 weeks. Overall, 90.7% of patients were treated within 8 weeks. Of patients receiving four cycles, the median duration of chemotherapy was 8.9 weeks, with a minimum duration of 8.6 weeks and a maximum duration of 11.7 weeks. All patients completed chemotherapy within 12 weeks.

Radiation Therapy

Seven patients were treated with adjuvant radiation therapy after chemotherapy, at a median interval of 10.4 weeks with a minimum interval of 8.6 weeks and a maximal interval of 15.9 weeks. The mediastinum of each of these patients harbored disease, and two also had positive margins. A single patient was treated before chemotherapy, at an interval of 7.9 weeks after surgery, with chemotherapy 8.6 weeks later; this patient had a positive surgical margin but no mediastinal disease.

Toxicity

CDDP-Doc toxicity is summarized in Table 2. The most frequent grade ≥ 3 toxicity was febrile neutropenia. Overall, 8.5% of the 47 patients for whom toxicity data were available experienced febrile neutropenia. Of these 47 patients, 26 received up-front peg-filgrastim; none of these patients experienced this complication. Twenty-one patients did not receive peg-filgrastim and five, or 23.8% of these, sustained febrile neutropenia. Of these 5 patients, one died of febrile neutropenia. In seven patients, the use or lack of use of peg-filgrastim could not be confirmed from chart records. Additional grade 3 side effects included fatigue, nausea, and gastritis, affecting 6.4% of the patients each and diarrhea affecting 2.1%; there were no grade 4 toxicities. Of 29 patients who received up-front aprepitant, 86.2% experienced any grade nausea, and 34.5% experienced grade 2 or 3 nausea. Of 18 patients who did not receive up-front aprepitant, 83.3% experienced any grade nausea, and 22.2% experienced grade 3 nausea. Full toxicity data are shown in Table 2.

Outcomes

OS and PFS are shown in Figures 1 and 2. Overall median survival has not yet been reached, with actual 1-year survival of 85.2% and actual 2-year survival of 68.1% for patients with at least 2 years of follow-up. Median PFS was reached at 17.9 months, with 1 year actual PFS of 67.3% for patients with at least a year of follow-up for progression and 2 year PFS of 50% for those with at least 2 years of potential follow-up. Of note, follow-up for many surviving patients

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<td>4</td>
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<th>Toxicity of Therapy (%)</th>
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<tr>
<td>Fatigue</td>
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<td>Nausea</td>
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<td>Diarrhea</td>
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<td>Anemia</td>
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<td>Anorexia</td>
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<td>Emesis</td>
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<td>Constipation</td>
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<td>Myalgia</td>
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<td>Febrile neutropenia</td>
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<td>Gastritis</td>
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<td>Edema</td>
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<td>Tinnitus</td>
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<td>Bone pain</td>
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<td>Rash</td>
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<td>Infusion reaction</td>
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The values are given in percentages.
remains immature, creating divergence between actual outcomes and those estimated by Kaplan-Meier plots. Censoring is quantified by annotation of OS and PFS curves with number at risk.

In accordance with prespecified criteria, all patients treated with adjuvant CDDP-Doc were included in the analysis. Included in these results are seven patients who would not have been candidates for the formal adjuvant trials. Six patients had stage IIIb disease by virtue of T4 primary, and a single patient each had an isolated brain metastasis, two synchronous stage Ia primaries, PS2, and PS3. When these patients are excluded, 44 patients remain. In this population, 88.6% received four full cycles. For this population, median OS has not been reached, and mPFS is 15.4 months. Actual 1-year OS is 84.1%, and for those with at least 2 years elapsed since resection, 78.0% remain alive. For those with at least a year elapsed since resection, PFS is 79.5%, and for those with at least 2 years of follow-up data for progression, 50.0%.

DISCUSSION

To the best of our knowledge, this report represents the largest published study of the adjuvant treatment of NSCLC with cisplatin and Doc. Treatment was feasible, with 83.3% of patients receiving four full cycles of therapy and efficacy at least comparable with the large adjuvant studies of CDDP-vin. The study was neither prospective nor randomized. Rather, patients were selected for treatment for CDDP-doc based on the judgment of the treating physician and the willingness of the patient. This selection strategy is consistent with real-world, off-protocol, clinical decision making. The consequence of this is reflected in the demographic data—women, African Americans, and patients with T4 disease by satellite nodules are represented as are a patient with PS2, a patient with PS3, and a patient with two small primary tumors.

Cisplatin-containing doublets demonstrated a 5.4% absolute survival benefit in the LACE meta-analysis. The CDDP-vin combination yielded a higher survival benefit than other regimens, especially second generation regimens with vinca alkaloids and etoposide and those featuring mitomycin. The authors speculated that this difference may be due not to superiority of vin but rather to increased dose-delivery of cisplatin. Although cisplatin dose delivery may have been higher when combined with vin than with other regimens, dose delivery remained suboptimal. For example, only half of patients assigned to chemotherapy on the ANITA trial received all four cycles; and the median number of cycles delivered in JBR.10 was three. In contrast, 83.3% of patients in this series received four full doses. The importance of drug delivery has been accepted by many oncologists and has been well demonstrated in the adjuvant treatment of breast cancer.

The TAX326 study in advanced incurable NSCLC demonstrated higher dose delivery with CDDP-doc than with CDDP-vin at a median of five cycles with CDDP-Doc, when compared with a median of four cycles with CDDP-vin. This difference in dose delivery may partially explain the difference in efficacy reported in this trial. Patients treated with CDDP-doc lived a median of 11.3 months, compared with 10.1 months for CDDP-Vin (p = 0.044). Response rate was also higher for CDDP-doc at 31.6% compared with 24.5% for CDDP-Vin (p = 0.029). CDDP-Doc was also tolerable and efficacious in the Swiss Group for Clinical Cancer Research neo-adjuvant phase II study of stage IIIa patients. In this study, 96% of patients received at least three cycles, the response rate was 66% and median survival 33 months. In contrast, a small phase II study from Memorial Sloan Kettering Cancer Center (MSKCC) found CDDP-doc to be poorly tolerated in the adjuvant setting both in a cohort given weekly Doc and in another cohort given every 3-week Doc. Six of eleven patients were unable to complete three cycles in the every 3-week cohort. For some oncologists, this report engendered the notion that the CDDP-doc regimen is too toxic in the adjuvant setting.

We chose to query the lung cancer database of the Hospital of the University of Pennsylvania in response to both this controversy and the inclusion of this regimen in the ongoing Eastern Cooperative Oncology Group (ECOG)1505 trial. To date, the distribution of regimens used in E1505 has not been reported; in addition to “standard” CDDP-vin, enrollees may receive CDDP-doc, as well as CDDP-gemcitabine and CDDP-pemetrexed.
The population reported in our series contains a relatively high proportion with advanced disease and has an overall worse PS than the trials described in Table 3. All six patients with stage IIIb disease qualified for this designation through T4 stage and not N3 stage. As such, we considered them appropriate for curative-intention surgery. Indeed, the seventh edition of the TNM staging system will reclassify these patients at T3 and thus stage IIB-IIIA, reflecting the potential for cure. Similarly, we consider the patient with a solitary metastasis potentially curable. Finally, some may assume that the prognosis of these patients and those with PS2–3 or multiple primary cancers would be expected to be worse than patients with earlier-stage disease. This assumption did not bear out in our analysis—when these 10 patients were excluded, 88.6% of the remaining patients received four full cycles of therapy with similar survival and freedom from progression. We note that these patients were not randomized but rather selected by the treating physicians at a weekly multidisciplinary thoracic tumor board. We believe that personalized therapy through multidisciplinary collaboration was key to achieving these results and strongly endorse the practice.

In addition to dose-delivery, patient convenience is increased with the CDDP-Doc regimen as compared with CDDP-Vin, since treatment is administered every 3 weeks, rather than on days 1 and 8 as in ANITA or weekly for 16 weeks as in JBR.10. Survival cannot be directly compared with the major adjuvant trials but is within the expected outcomes for this population. Feasibility and toxicity are comparable with the CDDP-Doc arm of a randomized trial presented at the World Lung Conference in 2009 comparing adjuvant CDDP-Doc to CDDP-Gemcitabine.10

Although our database does not capture toxicity beyond the surrogate measures of number of cycles delivered, we were able to definitively evaluate toxicity from chart review in 47 patients. In the MSKCC trial, severe fatigue was the dose-limiting toxicity in four patients. Fatigue was the second most common grade 3/4 toxicity in our series, affecting 6.4% of patients. Aggressive maintenance of optimal volume status with home intravenous fluids, if necessary, along with a tapering dose of steroids following the recommended dexamethasone preparation have both been helpful in mitigating this issue. One patient was limited by nausea in the MSKCC study despite an aggressive and appropriate antiemetic regimen. Overall, 6.4% of our patients were also affected by grade 3/4 nausea.

Finally, one of 11 patients in the Q3 week cohort of the MSKCC trial developed fever and neutropenia. We routinely used prophylactic pegylated filgrastim when feasible and noted no febrile neutropenic events in the 26 of 47 (55.3%) of patients who received primary prophylaxis with pegylated filgrastim. In contrast, 23.8% of the 21 patients who did not receive pegylated filgrastim experienced febrile neutropenia. One of these patients died after initially refusing admission for intravenous antibiotics. In the TAX326 study of CDDP-doc in the metastatic setting, patients did not receive primary prophylaxis but were permitted to receive secondary prophylaxis. Overall, 74.8% experienced grade 3/4 neutropenia, defined as absolute neutrophil count < 1000; however, only 4.8% experienced febrile neutropenia. A similar percentage of patients (69%), on the CDDP-doc arm of ECOG 1594,11 experienced grade 3/4 neutropenia with 11% of the total cohort experiencing febrile neutropenia. This 11% figure is identical to the overall incidence in our analysis. ECOG and National Comprehensive Cancer Network (NCCN) guidelines both recommend primary prophylaxis if the risk of febrile neutropenia reaches 20%.12,13 As the rate of febrile neutropenia in patients not treated with prophylactic pegylated filastim reached 23.8% in our series, routine use of primary prophylactic pegylated filgrastim would be consistent with these recommendations.

CDDP-doc is not the right regimen for every adjuvant patient. Our database captured 102 patients treated with at least one cycle of adjuvant chemotherapy during the period studied, with just over half receiving CDDP-Doc. Overall, 66.7% of the remaining 44 patients were treated with non-cisplatin regimens with typical reasons including renal insufficiency, impaired hearing, preexisting neuropathy, and desire to avoid nausea, and 52.1% chose treatment with gemcitabine or pemetrexed, mostly from a preference to avoid alopecia. Of note, some patients fit into both of these categories and were thus treated with a non-cisplatin, non-Doc regimen. Treatment decisions incorporating the comorbid conditions and expectations of the patient are an important part of quality care.

The HUP series is relatively small and retrospective in nature. Patients were selected for eligibility by the decision of the treating physicians. Thus, advanced disease stage and comorbidity are more substantial than in the major adjuvant studies; however, alternative sources of selection bias may be present. Toxicity data were retrospectively coded to CTCAE v4. Although chart records were quite detailed, it is possible

### Table 3. Select Relevant Adjuvant Trials in NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Stage</th>
<th>PS</th>
<th>Cycles Delivered</th>
<th>N</th>
<th>mOS</th>
</tr>
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<tbody>
<tr>
<td>ANITA</td>
<td>CDDP: 100 mg/m² × 4 and Vin: 30 mg/m² × 16</td>
<td>I: 36%, II: 22%, IIIa: 41%, and IIIb-IV: &lt;1%</td>
<td>WHO—0: 48%, 1: 47%, and 2: 3%</td>
<td>50% received four cycles</td>
<td>840</td>
<td>65.7 mo</td>
</tr>
<tr>
<td>JBR.10</td>
<td>CDDP: 50 × 2 mg/m² and Vin 25 mg/m² × 16</td>
<td>Ib: 45% and II: 55%</td>
<td>ECOG—0: 50% and 1: 50%</td>
<td>Median of three cycles</td>
<td>242</td>
<td>94 mo</td>
</tr>
<tr>
<td>MSKCC</td>
<td>CDDP: 75 mg/m² and Doc: 80 mg/m²</td>
<td>IB: 18%, IIa: 18%, IIb: 37%, IIIa: 9%, and IIIb: 18%</td>
<td>Karnofsky 80%: 45% and Karnofsky 90%: 55%</td>
<td>55% unable to complete three cycles</td>
<td>11</td>
<td>Not reached at 18 mo follow-up</td>
</tr>
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WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; MSKCC, Memorial Sloan Kettering Cancer Center.
that minor toxicities were not recorded in the charts and that
the extent of toxicity may be under or over estimated retro-
spectively. Blood counts were not checked at nadir, resulting
in likely undercapture of cytopenias that did not result in
symptomatic toxicity. Finally, survival cannot be directly
compared with the major adjuvant trials because of different
methods of patient selection.

The ongoing ECOG1505 trial compares adjuvant chemother-
apy with or without bevacizumab. The choice of CDDP
doublet is left to the discretion of the treating physician, with
choice of partner agents including vin, Doc, gemcitabine, and,
by recent amendment, pemetrexed. There are very little pub-
lished data on regimens other than vin and cisplatin in this
setting. Hence, our review, although relatively small, shows that
combination CDDP and Doc in this setting is safe and feasible;
and based on preliminary outcome data, it is likely to generate
similar efficacy to the vin-cisplatin regimen.

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