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A Phase II Tolerability Study of Cisplatin Plus Docetaxel as Adjuvant Chemotherapy for Resected Non-small Cell Lung Cancer

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Abstract

Introduction—We undertook this phase II study to measure postoperative drug delivery and toxicity of cisplatin plus docetaxel in patients with resected stage I-III non-small cell lung cancer.

Methods—The primary endpoint was amount of cisplatin delivered over a planned four cycles of adjuvant chemotherapy. Statistical design required a cohort to close if the regimen proved unlikely to improve cisplatin delivery compared with published phase III data. The first cohort was treated with docetaxel 35 mg/m^2 intravenously (IV) on days 1, 8, and 15, and cisplatin 80 mg/m^2 IV on day 15, every 4 weeks for four planned cycles. A second cohort was treated with docetaxel 75 mg/m^2 IV plus cisplatin 80 mg/m^2 IV on day 1 every 3 weeks for four planned cycles.

Results—Sixteen patients were treated with weekly docetaxel and cisplatin every 4 weeks, with five of 16 (31%) unable to complete three cycles. Subsequently, 11 patients were treated with docetaxel and cisplatin every 3 weeks, with six of 11 (55%) unable to complete three cycles. Among the 11 patients who failed to complete three cycles, the reasons for stopping included one or more of the following: fatigue (n = 8), nausea (n = 4), febrile neutropenia (n = 1), hypotension (n = 1), and nephrotoxicity (n = 1).

Conclusions—The combination of cisplatin at 80 mg/m^2 with docetaxel 35 mg/m^2 weekly or 75 mg/m^2 every 3 weeks is no better tolerated than older chemotherapy regimens. The most common reason to stop chemotherapy was intolerable fatigue. These results suggest that the most common dose-limiting toxicities are attributable to the cisplatin, given similar problems were encountered whether the docetaxel was delivered as a single dose every 3 weeks or as a lower weekly dose.

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Keywords

Non-small cell lung cancer; Adjuvant chemotherapy; Cisplatin; Docetaxel

Cisplatin-based chemotherapy after surgical resection of stage IB-III non-small cell lung cancer (NSCLC) improves survival over surgery alone. Three recent randomized studies have demonstrated a reduction in the risk of death of 14% to 30%.[1–3] A meta-analysis of five contemporary trials randomizing over 4500 patients suggested that higher stage patients derived greater reduction in their risk of death, with clear benefit in stage II-III disease (hazard ratio [HR] = 0.83, 95% confidence interval: 0.73– 0.95), and borderline benefit in IB patients (HR = 0.92, 95% confidence interval: 0.78– 1.1).[4] The three clinical trials that most clearly demonstrated this benefit were launched in 1994 to 1995, and the majority of patients treated in the experimental arm received a combination of cisplatin plus vinorelbine, considered to be the most effective, least toxic chemotherapy available at the time.

These three trials each planned to deliver four cycles of chemotherapy over approximately 4 months using a variety of drugs, doses, and schedules. The International Adjuvant Lung Trial (IALT) allowed investigators to choose between cisplatin at 80 mg/m^2 intravenously (IV) every 3 weeks (q3wk), 100 mg/m^2 q4wk, or 120 mg/m^2 q4wk in combination with either etoposide 100 mg/m^2 IV daily for 3 days per cycle or vinorelbine 30 mg/m^2 IV weekly or vinblastine 4 mg/m^2 IV weekly or vindesine 3 mg/m^2 IV weekly.[2] The majority of patients received cisplatin with etoposide (56%), and the second most employed regimen was cisplatin with vinorelbine (27%). Overall, 74% of patients received ≥240 mg/m^2 total dose of cisplatin in the IALT study. Patients treated on the ANITA trial (Adjuvant Navelbine International Trialist Association) received cisplatin 100 mg/m^2 IV q4wk with vinorelbine 30 mg/m^2 IV weekly. Sixty-one percent of patients completed at least three cycles (≥300 mg/m^2 total cisplatin dose).[3] Patients on the NCIC (National Cancer Institute of Canada) BR10 trial received cisplatin 50 mg/m^2 IV on days 1 and 8, with vinorelbine 25 mg/m^2 IV weekly with 58% of patients completing at least three cycles (≥300 mg/m^2 total cisplatin dose).[1] By administering the cisplatin in this manner, lower rates of grade 3–4 fatigue (15% versus 28%), nausea (10% versus 27%), and treatment-related deaths (1% versus 2%) were observed compared with ANITA.[1,3] However, this approach did not appear to improve drug delivery in that similar proportions of patients completed one, two, three, and four cycles of chemotherapy in both BR10 and ANITA. The IALT investigators reported the highest proportion of patients (74%) completing at least three cycles of adjuvant chemotherapy.

A fundamental principle of adjuvant therapy is that improving drug delivery, either total dose or dose density, should improve efficacy. This concept has been shown to be important to the adjuvant therapy of breast cancer.[5] The IALT, the only individual trial to use a variety of drug regimens, found no significant interaction between survival benefit from adjuvant chemotherapy and cisplatin dose (dose per cycle or total dose) or drug combined with cisplatin (etoposide or vinca alkaloids).[2] This is not surprising given this was a subgroup analysis in a trial with a small level of survival benefit.

Using pooled data and meta-analysis, some hypotheses can be generated regarding drug delivery. A pooled analysis of all patients randomized to receive adjuvant vinorelbine plus cisplatin (four trials, $n = 1888$) demonstrated a highly significant benefit for this regimen in the adjuvant setting (HR = 0.80, 95% confidence interval: 0.70–0.91, $p = 0.0007$).[6] A larger meta-analysis (five trials, $n = 4584$) allowed comparison of this regimen with other two- and three-drug cisplatin combinations and demonstrated that cisplatin plus vinorelbine was more effective than other drug combinations tested (HR = 0.80 versus 0.93 for other two-drug

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combinations and 0.98 for other three-drug combinations).[4] The authors noted that the cisplatin plus vinorelbine combination allowed for a higher total dose of cisplatin to be delivered than the other combinations, with the majority of patients offered a planned total dose of as high as 400 mg/m^2. Thus, the authors concluded that the lower benefit with other cisplatin combinations may be due to the lower cisplatin dose.[4]

Randomized trials in patients with metastatic NSCLC suggest that cisplatin combinations using third-generation drugs (docetaxel, gemcitabine, and paclitaxel) may be superior to older regimens.[7–9] These trials lead to U.S. Food and Drug Administration approval of these new drugs in combination with cisplatin as first-line chemotherapy for patients with incurable metastatic NSCLC.

Between 1998 and 2000, a phase III trial was conducted comparing cisplatin plus vinorelbine with cisplatin plus docetaxel as first-line chemotherapy in more than 800 patients with metastatic NSCLC.[9] In this trial, vinorelbine 25 mg/m^2 IV weekly was given with cisplatin 100 mg/m^2 IV q4wk. Docetaxel was delivered at 75 mg/m^2 IV with cisplatin 75 mg/m^2 IV administered on the same day every 3 weeks. The results of this trial demonstrated that docetaxel plus cisplatin was superior to vinorelbine plus cisplatin in terms of radiographic response rate (32% versus 25%, $p = 0.029$), and overall survival (median survival time, 11.3 versus 10.1 months, $p = 0.044$).[9] There were significantly less grade 3–4 nausea, vomiting, and anemia and improved quality of life in the docetaxel plus cisplatin arm compared with the vinorelbine plus cisplatin arm.[9] Despite similar proportions of patients being taken off study for disease progression, patients in the docetaxel plus cisplatin arm received a higher relative dose intensity than vinorelbine plus cisplatin (0.94 versus 0.78). These data in metastatic patients suggest that the combination of cisplatin plus docetaxel might improve drug delivery and possibly outcomes in the postoperative setting as well.

Similarly, a 230-patient randomized phase II comparison of cisplatin plus vinorelbine with cisplatin plus docetaxel in patients with metastatic NSCLC documented numerically superior radiographic response rate, and 2- and 3-year survival proportion for docetaxel, although the sample sizes were too small to reach statistical significance. Cisplatin plus docetaxel also appeared to be safer and better tolerated, with less febrile neutropenia (10% versus 26%), less treatment-related mortality (2% versus 8%), fewer instances of dose delay, and a higher relative dose intensity achieved.[10] A meta-analysis of seven randomized trials ($n = 2867$) comparing docetaxel and vinca alkaloids, alone or in combination with other chemotherapy agents, in the first-line treatment of metastatic NSCLC demonstrated superior survival with the use of docetaxel (HR = 0.89, 95% confidence interval: 0.82– 0.96, $p = 0.03$), along with lower rates of neutropenia (OR = 0.60, 95% confidence interval: 0.39–0.92) and febrile neutropenia (OR = 0.60, 95% confidence interval: 0.39–0.96).[11]

Based on these data, we hypothesized that a combination of cisplatin plus docetaxel would be a good alternative to the chemotherapy used in IALT for the adjuvant treatment of patients with completely-resected NSCLC. Assessment of toxicity and drug delivery of cisplatin plus docetaxel in this study would serve as a prelude to randomized trials comparing docetaxel to vinorelbine in combination with cisplatin postoperatively. We also hypothesized that cisplatin plus docetaxel would result in better tolerance of chemotherapy, and allow for delivery of a higher total dose of cisplatin compared to published data (IALT). In addition to patient selection, we were conscious of a number of dependent variables which could have an impact on cisplatin delivery, including the dose of cisplatin per cycle, the amount of time between each dose of cisplatin, the dose of docetaxel delivered with cisplatin, and the use of ancillary or supportive medications such as antiemetics or hematopoietic growth factors. Several randomized studies in patients with metastatic

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NSCLC have demonstrated that docetaxel may be delivered at a lower dose, on a weekly schedule, with lower rates of fatigue and neutropenia and no apparent loss of efficacy.[12] Furthermore, studies combining gemcitabine with cisplatin suggest that dose delivery and intensity are best maintained by delivering cisplatin at the end of the treatment cycle rather than on day 1.[13,14]

PATIENTS AND METHODS

This was an investigator-initiated, two-institution phase II trial conducted between November 2004 and August 2006 at Memorial Sloan-Kettering Cancer Center, Department of Medicine, Thoracic Oncology Service in New York, NY, and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD. The primary efficacy outcome variable was total cisplatin dose delivered.

Our null hypothesis was that docetaxel plus cisplatin would be no better tolerated than the chemotherapy delivered in the IALT. In IALT, 74% of patients were able to tolerate ≥240 mg/m^2 of cisplatin. If ≤75% of patients were able to tolerate more than three cycles of docetaxel/cisplatin chemotherapy, then this regimen would be no better tolerated than historical chemotherapy. If 90% or more patients completed all four cycles of docetaxel/cisplatin, then this regimen would be considered more tolerable. Using a two-stage design, we planned to enroll 16 patients on each cohort. If <12 patients tolerated more than three cycles of chemotherapy, then the trial would be stopped. If >12 patients tolerated more than three cycles of chemotherapy, the trial would be expanded to 50 patients. If >40 patients tolerated more than three cycles, then the null hypothesis would be rejected (α = 10%, β = 10%).

The first dosing schedule tested delivered docetaxel 35 mg/m^2 IV on days 1, 8, and 15, plus cisplatin 80 mg/m^2 IV on day 15, every 4 weeks for a planned four cycles. Eligible patients were within 2 months of their lung surgery, had complete resection of stage IB-III NSCLC, had not received any previous chemotherapy or postoperative radiation therapy, and had adequate hematologic, hepatic, and renal function. Patients received dexamethasone 8 mg orally the evening before, morning of, and evening after docetaxel. Before and after cisplatin, patients received acute and delayed emesis prophylaxis including a 5-HT3 receptor antagonist (palonosetron on day 1 or ondansetron, granisetron, or dolasetron on days 1–3), dexamethasone (12 mg orally (PO) on days 1–3), and aprepitant (125 mg PO on day 1, 80 mg PO on days 2 and 3). Patients received standard hydration on days of cisplatin administration, including instructions to drink 1 to 2 liters of extra fluid the evening before cisplatin, 1 liter of IV normal saline before cisplatin, an additional liter IV after cisplatin, and instructions to drink 2 liters of extra fluid overnight after cisplatin. In the days that followed, patients were given metoclopramide 10 mg PO every 4 hours, prochlorperazine 10 mg PO every 6 hours, or lorazepam 1 mg PO every 4 hours as needed for delayed nausea or vomiting. Prophylactic use of granulocyte growth factors was not permitted. Standardized dose reductions of docetaxel and/or cisplatin in subsequent cycles were based on observed toxicities. Patients received darbepoetin for chemotherapy-induced anemia if appropriate.

A second cohort tested docetaxel 75 mg/m^2 IV plus cisplatin 80 mg/m^2 IV on day 1 every 3 weeks for a planned four cycles. Due to the higher risk of neutropenia with this regimen, prophylactic use of hematopoietic growth factors (pegylated filgrastim) was allowed beginning with cycle 2 if appropriate.

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RESULTS

Between August 2004 and June 2006, 27 patients were enrolled in this study; 16 received weekly docetaxel and monthly cisplatin, 11 received docetaxel with cisplatin every 3 weeks. Patient characteristics are summarized in Table 1.

Drug Delivery

Cisplatin delivery and dose limiting toxicities are summarized in Table 2.

The first cohort testing weekly docetaxel was closed early when only 11 of the first 16 patients (69%) were able to tolerate ≥240 mg/m^2 of cisplatin, making it statistically unlikely that this regimen would prove to be better tolerated than the chemotherapy regimens used in IALT. The most common dose-limiting toxicity was fatigue, which limited drug delivery in four of the five patients who dropped out before receiving 240 mg/m^2 of cisplatin. Nephrotoxicity limited drug delivery in the fifth patient, and one patient was limited by both fatigue and nausea.

We hypothesized that the fatigue may have been related to the cumulative effects of two doses of docetaxel on days 1 and 8, leading up to combination of docetaxel and cisplatin on day 15. Therefore, we amended the protocol to explore the toxicity of docetaxel plus cisplatin every 3 weeks, which had the advantage of longer recovery times between cisplatin doses and fewer treatment days. In this second cohort, only five of 11 patients treated (45%) were able to tolerate ≥240 mg/m^2 of cisplatin, and this cohort was also closed to accrual. Once again, the most common dose-limiting toxicity was fatigue, which limited drug delivery in four of the six patients who dropped out. Other dose-limiting toxicities included nausea (n = 1) and febrile neutropenia with hypotension (n = 1). Two patients were limited by both fatigue and nausea.

The median cisplatin delivery was 240 mg/m^2 in both cohorts (range, 80–380 mg/m^2). Of note, patients who received weekly docetaxel and monthly cisplatin received more docetaxel and completed their chemotherapy in 16 weeks. Patients who received docetaxel and cisplatin every 3 weeks received less docetaxel, but completed their chemotherapy in 12 weeks, thereby achieving a higher dose density of cisplatin.

Toxicity

There were no treatment-related deaths. Twelve of 27 patients (44%) experienced a serious adverse event related to study treatment, including admissions to the hospital for nausea requiring intravenous fluids (n = 5), pleural effusion (n = 2), supraventricular tachycardia (n = 2), febrile neutropenia (n = 1), diarrhea (n = 1), and hypersensitivity (n = 1). Observed grade 3–4 toxicities are summarized in Table 3. In both cohorts, the most common reason for stopping adjuvant therapy was intolerable fatigue, which typically occurred after the first cycle of chemotherapy.

Efficacy

Twenty-seven patients have been treated with adjuvant cisplatin plus docetaxel, with a median follow-up of 18 months (range, 4–26). As of August, 2006, two patients have died, both due to recurrent NSCLC (stages IIIA and IIIB). Three other patients (stages IIIA, IIA, IB) have experienced recurrence of NSCLC and remain alive. Median disease- free and overall survival times have not been reached.

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DISCUSSION

Based on available data, cisplatin plus vinorelbine is the best and most studied drug regimen for adjuvant treatment of NSCLC. Randomized trials to establish alternative or superior chemotherapy will require large sample sizes and years of follow-up. Meanwhile, the list of promising drugs for the treatment of metastatic NSCLC continues to grow.

In 1994, vinorelbine was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic NSCLC, both as a single agent and in combination with cisplatin. Since the positive adjuvant trials were launched in 1995, there have been three additional drugs approved by the FDA in combination with cisplatin for first-line therapy of metastatic NSCLC (paclitaxel, gemcitabine, and docetaxel). There are also drugs in common use based on phase III efficacy (most notably carboplatin), which have not been FDA approved. Many phase III comparisons of two-drug, cytotoxic combinations in patients with metastatic NSCLC have shown relative equivalence in efficacy among cisplatinbased, carboplatin-based, and nonplatinum combinations.[9,15–18] Recent meta-analyses suggest that cisplatin combinations are superior to carboplatin combinations in terms of response rate and survival.[19,20] These data suggest that cisplatin should be included as part of a planned adjuvant regimen.

There are three drugs that have been shown to improve survival as single-agents in second-line therapy for metastatic NSCLC: docetaxel, erlotinib, and pemetrexed. To date, only one targeted therapy, the anti–vascular endothelial growth factor agent bevacizumab, has improved survival for selected patients with metastatic NSCLC when given in combination with chemotherapy compared with chemotherapy alone.[21] The efficacy of bevacizumab in the adjuvant setting will be examined in the upcoming intergroup randomized adjuvant trial, Eastern Cooperative Oncology Group (ECOG) 1505.[22] In addition to bevacizumab, numerous other molecularly targeted drugs with demonstrated activity in metastatic NSCLC are on the horizon.

Given the pace with which new drugs are being developed, it is difficult or impossible to test them all in the adjuvant setting. ECOG has gone so far as to intuitively adopt regimens for adjuvant therapy based on data in metastatic patients. The treatment regimens for the ECOG 1505 intergroup adjuvant trial are docetaxel/cisplatin, gemcitabine/cisplatin, and vinorelbine/cisplatin, all given alone or in combination with bevacizumab.[22] These regimens were adopted based on efficacy data in the metastatic setting and to allow for a variety of regimens to enhance accrual to the trial. A carboplatin-based regimen was not included given meta-analyses of trials in metastatic NSCLC, suggesting inferiority compared with cisplatin and the lack of positive clinical trial data using anything but cisplatin combinations in the adjuvant setting.[23] At this time, carboplatin should not be routinely recommended as part of an adjuvant regimen.

The adoption of regimens for use in the adjuvant setting in the absence of data is innovative and unfounded. There are examples in other disease types in which chemotherapy regimens of superior efficacy in the metastatic setting proved to be no better or even harmful in the adjuvant setting. For example, novel combinations of fluorouracil and irinotecan, which have been shown to be superior to fluorouracil alone for the treatment of metastatic colon cancer,[24] repeatedly failed in the adjuvant setting due to increased toxicity and lack of clinical benefit.[25–27] Similarly, there are data that suggest that docetaxel is superior to paclitaxel for metastatic breast cancer[28]; however, paclitaxel and docetaxel have equivalent efficacy, with higher toxicity for docetaxel when given after doxorubicin and cyclophosphamide in the adjuvant treatment of breast cancer.[29] Conversely, novel

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combinations of docetaxel and cyclophosphamide are less toxic and more effective than doxorubicin and cyclophosphamide in the adjuvant setting.[30]

The design of our trial rested on the assumption that drug delivery is an important determinant of the effectiveness of adjuvant chemotherapy for NSCLC and that drug delivery is a reasonable endpoint for a phase II tolerability study. The results of a randomized trial comparing docetaxel/cisplatin with vinorelbine/cisplatin in patients with metastatic NSCLC suggested that the combination docetaxel/cisplatin was superior in terms of drug delivery, response rate, and survival.[9] The median number of treatment cycles delivered was five over 15 weeks for docetaxel/cisplatin and four over 16 weeks for vinorelbine/cisplatin, with a lower relative dose intensity for vinorelbine/cisplatin (0.94 versus 0.78). Similar proportions of patients were taken off study for disease progression (30% in both arms). These data are corroborated by randomized phase II data showing similar trends in drug delivery, response rate, and survival between these two regimens.[10] However, patients with NSCLC who have recently undergone surgery are clearly a different population than patients with metastatic NSCLC and may exhibit a different tolerance and side effect profile.

This is the first clinical trial to test the tolerability of docetaxel/cisplatin in the adjuvant setting. Our trial was designed to demonstrate that docetaxel/cisplatin delivered to patients with completely resected NSCLC allowed a higher total dose of cisplatin than with the chemotherapy regimens used in IALT (including cisplatin combined with etoposide, vinorelbine, vindesine, and vinblastine). As a result of early closure due to poor drug delivery, the sample size of this trial is small ($n = 27$). Nevertheless, conclusions can be drawn regarding dose-limiting toxicities, which have immediate implications for patients treated with this regimen.

Our data suggest that the combination of cisplatin at 80 mg/m^2 IV with weekly docetaxel (35 mg/m^2) IV or docetaxel (75 mg/m^2) IV every 3 weeks is no better tolerated than chemotherapy regimens used in IALT. The most common reason to stop postoperative cisplatin and docetaxel was intolerable fatigue, which most often occurred after the first cycle. Neutropenia was seldom an issue in early discontinuation of therapy on either schedule. The every 3 weeks docetaxel plus cisplatin regimen is more amenable to the routine use of filgrastim, or pegylated filgrastim, to prevent neutropenia compared with weekly chemotherapy regimens. In this study, only four of 11 patients on the every 3 weeks cohort (36%) required treatment with pegylated filgrastim. Eleven of 27 patients treated in either cohort (41%) required treatment with darbepoetin. Despite using state-of-the-art acute and delayed emesis prophylaxis, seven patients (26%) experienced grade 3–4 nausea, and it was dose limiting in six patients. This is not unexpected, as the addition of aprepitant to standard antiemetics had little effect on the prevention of nausea in randomized trials.[31,32]

In this study, fatigue was the dose-limiting toxicity in eight of 11 patients who dropped out early, and 30% of all patients treated experienced grade 3–4 fatigue. The published adjuvant trials report rates of grade 3–4 fatigue as high as 28% using high-dose cisplatin with vinorelbine.[3] In patients with metastatic NSCLC treated with cisplatin plus docetaxel or vinorelbine, grade 3–4 fatigue was reported in only 12% to 14% of patients.[9,10] Clearly, patients immediately postoperatively are more susceptible to fatigue from cisplatin-based chemotherapy than patients with metastatic NSCLC.

Of note, grade 3–4 fatigue occurred less frequently in the BR10 trial (compared with ANITA) in which cisplatin was administered as a split dose with 50 mg/m^2 IV given on days 1 and 8 of each monthly cycle, with weekly vinorelbine. Despite lower rates of fatigue and nausea with this approach, similar proportions of patients completed one, two, three, and

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four cycles of chemotherapy in ANITA and BR10. Our trial did not explore whether split-dose cisplatin might mitigate fatigue or improve drug delivery in combination with docetaxel.

Based on our phase II data and the phase III adjuvant data using cisplatin plus vinorelbine, it is anticipated that approximately one half of patients will be unable to receive all four planned chemotherapy cycles in the intergroup adjuvant study (ECOG 1505). Treatment with split-dose cisplatin is not an option in ECOG 1505. Drug delivery will likely be even lower in the experimental arm of the study as the coadministration of bevacizumab will lead to increased toxicity, particularly neutropenia, hypertension, venous and arterial thrombotic events, and toxic deaths.

In conclusion, docetaxel plus cisplatin was difficult to deliver in the postoperative setting in this phase II trial. The most common dose-limiting toxicities are more likely attributable to cisplatin rather than the docetaxel, given that the same problems were encountered whether the docetaxel was delivered at a single high or lower weekly dose. These results predict difficulty in delivering cisplatin and docetaxel in both the control and experimental treatment arms of ECOG 1505. The results of ongoing randomized trials comparing preoperative versus postoperative delivery of docetaxel/cisplatin will be of significant interest. Priority should be given to developing noncisplatin adjuvant regimens for evaluation in a phase III trial.

The therapeutic benefit of adjuvant chemotherapy should be enhanced through identification of more efficacious regimens and alternatives to cisplatin-based therapy. As demonstrated in this study, many patients prove intolerant to cisplatin and cannot complete prescribed therapy. Others are not candidates for cisplatin due to comorbid medical illness. In the future, the development of better prognostic molecular tests will allow low-risk patients to be spared adjuvant therapy, [23] and better predictive molecular tests may allow molecularly tailored adjuvant therapies. Recent research has identified subpopulations of patients who are inherently resistant to cisplatin-based chemotherapy. For example, overexpression of the DNA repair protein ERCC1 (excision repair cross-complementation group 1) in the resected tumor predicted a lack of benefit from adjuvant cisplatin, theoretically due to de novo resistance of the cancer to cisplatin-induced DNA damage.[33] Selection of noncisplatin regimens for these patients may improve outcome, and a phase II tolerability study of vinorelbine plus docetaxel in ERCC1-positive patients is planned for possible evaluation in a phase III trial.

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TABLE 1

Patient Characteristics

	Weekly Docetaxel and Cisplatin (*n* = 16)	Every 3 wk Docetaxel and Cisplatin (*n* = 11)
Median age, yr (range)	64 (47–71)	63 (42–71)
Women, no. (%)	8 (50)	6 (55)
Karnofsky performance status, no. (%)		
80%	1 (6)	5 (45)
90%	15 (94)	6 (55)
Type of surgery, no. (%)		
Lobectomy	15 (94)	9 (82)
Pneumonectomy	1 (6)	1 (9)
Wedge resection	0	1 (9)
Stage, no. (%)		
IB	5 (31)	2 (18)
IIA	3 (19)	2 (18)
IIB	1 (6)	4 (37)
IIIA	5 (31)	1 (9)
IIIB	2 (13)	2 (18)
Histology, no. (%)		
Adenocarcinoma	8 (50)	8 (73)
Squamous carcinoma	2 (13)	2 (18)
Adenosquamous	3 (19)	1 (9)
Large cell	1 (6)	0
Poorly differentiated	1 (6)	0
Bronchioloalveolar	1 (6)	0
Days from surgery to 1st chemotherapy (range)	50 (22–55)	50 (40–79)

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TABLE 2

Cisplatin Delivery

Total Cisplatin Dose Delivered (mg/m^2)	*n*	Dose-Limiting Eevent (grade 2–4)[a]
Weekly docetaxel and cisplatin		
>320	8	None
240	3	Fatigue (2), neuropathy (1), diarrhea (1), disease progression (1)
81–220	3	Fatigue (2), nephrotoxicity (1), nausea (1)
80	2	Fatigue (2)
Docetaxel and cisplatin every 3 wk		
320	4	None
240	1	Nausea (1)
81–220	2	Fatigue (1), nausea (1)
80	4	Fatigue (3), nausea (2), febrile neutropenia (1), hypotension (1)

[a]Some patients experienced more than one dose-limiting toxicity or event.

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TABLE 3

Observed Grade 3–4 Toxicity

	Weekly Docetaxel and Cisplatin (*n* = 16)	Every 3 wk Docetaxel and Cisplatin (*n* = 11)
Fatigue	5	3
Neutropenia	1	3
Nausea	4	3
Diarrhea	3	0
Hypersensitivity	2	0