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Phase II Study of Docetaxel and Vinorelbine as Adjuvant Chemotherapy for Resected Non-small Cell Lung Cancers

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Abstract

Purpose—For patients with resected stage II-III non-small cell lung cancers (NSCLCs), adjuvant cisplatin-based chemotherapy improves survival over surgery alone. For cisplatin ineligible patients, there is no standard adjuvant option. We evaluated drug delivery and toxicity of docetaxel and vinorelbine in patients who could not receive cisplatin.

Methods—Patients with completely resected stage IB-III NSCLCs were treated with up to 4 cycles of docetaxel and vinorelbine at the recommended phase II dose. The primary endpoint was drug delivery compared to historical delivery of adjuvant cisplatin plus vinorelbine. Secondary endpoints were toxicity and feasibility.

Results—Twenty-five patients were enrolled. Overall, 13/25 (52%, 95% CI 34 – 70%) completed 4 cycles, and 19/25 (76%, 95% CI 60 – 87%) completed ≥ 3 cycles. Twenty of 25 patients (80%) experienced a Grade 3 or 4 adverse event.

Conclusions—Delivery of this dose and schedule of docetaxel and vinorelbine was difficult with a dose delivery comparable to cisplatin plus vinorelbine, and cisplatin plus docetaxel, used in this setting.

Keywords

vinorelbine; docetaxel; adjuvant chemotherapy; early-stage non-small cell lung cancer

Introduction

Four cycles of cisplatin-based chemotherapy is standard adjuvant therapy for patients with resected stage II-III non-small cell lung cancers (NSCLCs).[1] Multiple randomized clinical trials have demonstrated a 9–31% relative reduction in the risk of death with adjuvant cisplatin-based chemotherapy, most commonly a combination of cisplatin and vinorelbine.[2–5] In 2008, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis of 4,584 patients enrolled on 5 randomized clinical trials demonstrated a 16% relative reduction in the risk of death with adjuvant cisplatin-based chemotherapy in patients with

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resected stage II-III NSCLCs, borderline benefit in patients with stage IB disease, and no benefit for stage IA NSCLCs.[6]

The combination of cisplatin and vinorelbine has several dose-limiting toxicities, including neutropenia, fatigue, nausea, ototoxicity and nephrotoxicity. Despite enrollment of fit patients with a median age of about 60, only 50% of patients enrolled in phase 3 trials were able to complete 4 cycles of adjuvant cisplatin and vinorelbine.[4, 7] Phase II experience with adjuvant cisplatin and docetaxel at our institution (administered both weekly and every 3 weeks) found chemotherapy administration equally as difficult, with 31% unable to complete 3 of 4 planned cycles with weekly docetaxel, and 55% unable to complete 3 of 4 planned cycles with docetaxel administered every 3 weeks.[8]

In patients who have an absolute contraindication to cisplatin, such as allergy, renal insufficiency, or hearing impairment, or in those who have a borderline performance status increasing their susceptibility to treatment-related toxicities, there is no standard adjuvant therapy. Possible investigational therapeutic combinations include carboplatin-based, and non-platinum chemotherapy regimens.[9]

This study aimed to assess the feasibility of delivering 4 cycles of a non-cisplatin adjuvant chemotherapy regimen (docetaxel and vinorelbine) to patients with completely resected NSCLCs who were ineligible to receive cisplatin. As the goal of adjuvant therapy is cure, we endeavored to give the maximally tolerated dose of both agents tested in earlier trials in individuals with stage IV disease: docetaxel 60 mg/m^2 and vinorelbine 45 mg/m^2 every 2 weeks with pegylated-filgrastim support.

Patients and Methods

This study was a single-institution, phase II study approved by the Institutional Review Board and conducted between June 2008 and December 2011 at Memorial Sloan-Kettering Cancer Center. Patients had completely resected non-small cell lung cancers and were deemed by the treating physician to be ineligible for cisplatin-based adjuvant chemotherapy.

The primary endpoint was drug delivery as assessed by the proportion of patients who completed 4 cycles of chemotherapy. To constitute a full cycle, the patient must have completed 2 doses of both drugs, docetaxel (Taxotere®, Sanofi-Aventis) 60 mg/m^2 and vinorelbine 45 mg/m^2 every 2 weeks with pegylated-filgrastim support (Neulasta®, Amgen) 6 mg subcutenously. Secondary endpoints included dose intensity of chemotherapy delivered, as calculated by dose administered/dose planned x 100, dose density of vinorelbine (dose administered over time of study therapy), and toxicity as assessed by CTCAE version 3.0.

The protocol was designed to evaluate whether in patients who are deemed unfit for cisplatin or unlikely to benefit form cisplatin, this non-cisplatin containing adjuvant regimen of docetaxel and vinorelbine would improve drug delivery compared to adjuvant cisplatin and vinorelbine rates reported the NCIC JBR10 and ANITA trials, as assessed by the proportion of patients who completed 4 cycles of chemotherapy. The percentages of patients who completed 1–4 cycles in the published trials were NCIC JBR10: 1 – 80%, 2 – 68%, 3 – 58%, 4 – 48% and ANITA 1 – 90%, 2 – 72%, 3 – 61%, 4 – 49%.[4, 5] The planned sample size of 42 patients was chosen to allow distinction between a rate of completion of 45% (considered not worthy of further investigation) and a desirable completion rate of 65%, with a one-sided type I and type II error rates of 5% and 20%, respectively. With these parameters, the trial would be considered successful if at least 24 of the 42 patients enrolled competed 4 cycles of therapy. Disease free (DFS) and overall survival (OS) probabilities were estimated using the Kaplan-Meier method from the date of surgery. Patients were

followed until death or disease recurrence, whichever came first for disease free survival (recurrence) analysis and until death for the overall survival analysis. Patients who did not experience the event of interest were censored at the time of the last available follow-up.

The study was designed according to the recommended phase II regimen used in advanced NSCLCs.[10, 11] After signing informed consent, patients received docetaxel 60 mg/m^2 and vinorelbine 45 mg/m^2 intravenously on day 1. This regimen is considered to be dose-intense for patients with stage IV NSCLCs, and requires prophylactic pegylated filgrastim 6 mg subcutaneously on day 2 after each dose, and prophylactic antibiotics to reduce the risk of febrile neutropenia. The prophylactic antibiotic regimen was ciprofloxacin 500 mg orally twice daily for 7 days starting 48 hours after chemotherapy or an alternative antibiotic if ciprofloxacin allergic.[10] Treatment was repeated every 2 weeks with 2 doses of chemotherapy considered 1 cycle. Patients were prescribed standard dexamethasone premedication (4–8 mg orally the evening before, the morning of, and the evening after each dose of chemotherapy). A total of 4 cycles or 8 doses of chemotherapy were planned. Dose reductions, omissions and delays were allowed for toxicities as specified in the protocol.

Results

Between June 2008 and September 2011, 25 of a planned 42 patients were enrolled in this study. Patient characteristics are summarized in Table 1.

Drug Delivery

Early experience demonstrated that the original dose-intense regimen was not tolerable in the post-operative setting. Of the first 13 patients treated on study, 9 required reduction in the docetaxel dose prior to cycle 2 of 4 planned cycles. The reasons for the dose reductions were intolerable fatigue (n=5), neutropenia despite pegfilgrastim (n=2), epiphora (n=1), and neuropathy (n=1). These were all expected adverse events attributable to the chemotherapy. With dose reduction, 11/13 patients completed all 4 cycles of chemotherapy.

Thereafter, the protocol was amended and the starting dose was lowered to docetaxel 45 mg/m^2 and vinorelbine 45 mg/m^2 intravenously every 2 weeks. This dose reduction did not alter the statistical design of the protocol. The original design allowed for dose reductions with patients completing 4 cycles of chemotherapy still counting towards the protocol's primary endpoint of cycle delivery.

The number (%) of patients who completed 1, 2 and 3 cycles was 24 (96%), 23 (92%), and 19 (76%), respectively. 13 (52%) of patients (95% CI 34 to 70%) received all four cycles of vinorelbine and docetaxel, the primary study endpoint. The reduced dose of docetaxel (45 mg/m^2) was not more effectively delivered than the initial dose of docetaxel (60 mg/m^2). The median delivered dose intensity (delivered dose/planned dose x 100) was 88% (range 13 –100%) for vinorelbine for all patients, 84% [95% confidence interval (CI) 60–100] for docetaxel starting at 60 mg/m^2, and 78% [95% CI 47–100] for docetaxel starting at 45 mg/m^2 dose cohort. Treatment delays were common with a median treatment delay of each cycle by 1 week, range 0 – 6 weeks.

Toxicity

There were no treatment-related deaths. Twenty of 25 patients (80%) experienced a serious (Grade 3 or 4) adverse event classified as either probably or definitely related to study treatment. These toxicities included: neutropenia (15), anemia (4), febrile neutropenia (6), fatigue (10), hyperglycemia (3), epiphora (1), nausea/anorexia (1), neuropathy (1), pneumonitis (4), other dyspnea/cough (3), allergic reaction (1), venous thromboembolism (1), and vinca-associated pain crisis (1).

Efficacy

The median post-operative follow-up is 29 months (range, 5 – 43 months). Eight patients have experienced disease recurrence (3 stage III) and 5 of these patients have died. The 2-year disease free survival is 63% (95% CI 37 – 81%) and overall survival is 89% (95% CI 63 – 97%).

Discussion

A consistent theme in adjuvant chemotherapy trials in patients with resected NSCLCs is the inability to give the planned doses of the study drugs. Two of the three largest neoadjuvant chemotherapy trials in NSCLC, the National Cancer Institute of Canada (NCIC) JBR.10, and the Adjuvant Navelbine International Trialist Association (ANITA) studies, prescribed a planned 4 cycles of post-operative cisplatin and vinorelbine. Despite enrolling a relatively young and fit patient population with median age of 61 years in NCIC JBR.10 and 59 years in ANITA, only 50% of patients completed all 4 cycles of chemotherapy.[4, 7] In this current phase II trial, 52% of individuals completed 4 cycles, a comparable percentage to the cisplatin-based regimens studied in phase II and III trials, as summarized in Table 2.

Several non-platinum regimens have been demonstrated to be equivalent to platinum-based doublets in patients with advanced disease.[12–14] While not compared in a randomized fashion, the highest reported response rate of a non-platinum regimen in advanced disease is a phase II study of docetaxel and vinorelbine with an objective response in 51% of patients and median survival of 14 months.[10, 11] Drug delivery of chemotherapy in patients with stage IV disease is limited primarily by progression of disease, nevertheless the median number of treatments in the phase II study in patients with stage IV NSCLCs was 5 cycles (range 1 – 13 cycles).[14]

In patients with stage IV NSCLCs in whom the goal is not cure, but symptom and disease control, avoiding toxicity is an important consideration, especially when there is little difference in survival when using a less toxic regimen. However, in the adjuvant setting where the goal is cure, efficacy and drug delivery are critical and the risk-benefit analysis is fundamentally different. In this study, docetaxel and vinorelbine was poorly tolerated in the adjuvant setting, with 80% of our patients experiencing a grade 3 or 4 toxicity. The rate of grade 3 or 4 hematologic toxicities was comparable to the published cisplatin and vinorelbine trials (Table 2), although non-hematologic toxicity totals cannot be directly compared to ANITA or JBR.10 based on the data reported.[4, 5]

Conclusion

This study found that adjuvant vinorelbine and docetaxel was difficult to administer in the post-operative setting with frequent grade 3 or 4 toxicities. This delivery challenge was similar to the published experience with adjuvant cisplatin-based regimens. Alternative strategies, including predictive biomarkers are desperately needed to identify patients with resectable lung cancers who should be treated with chemotherapy and with which drugs to treat.

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References

1. NCCN Clinical Practice Guidelines in Oncology - Non-Small Cell Lung Cancer. Apr 11. 2012 Available at http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
2. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004; 350:351–360. [PubMed: 14736927]
3. Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol. 2010; 28:35–42. [PubMed: 19933916]
4. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006; 7:719–727. [PubMed: 16945766]
5. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005; 352:2589–2597. [PubMed: 15972865]
6. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008; 26:3552–3559. [PubMed: 18506026]
7. Alam N, Shepherd FA, Winton T, et al. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer. An analysis of National Cancer Institute of Canada and intergroup trial JBR. 10 and a review of the literature. Lung Cancer. 2005; 47:385–394. [PubMed: 15713522]
8. Azzoli CG, Krug LM, Miller VA, et al. A phase II tolerability study of cisplatin plus docetaxel as adjuvant chemotherapy for resected non-small cell lung cancer. J Thorac Oncol. 2007; 2:638–644. [PubMed: 17607120]
9. Pisters KM, Le Chevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol. 2005; 23:3270–3278. [PubMed: 15886314]
10. Miller VA, Krug LM, Ng KK, et al. Phase II trial of docetaxel and vinorelbine in patients with advanced non-small-cell lung cancer. J Clin Oncol. 2000; 18:1346–1350. [PubMed: 10715307]
11. Miller VA, Ng KK, Krug LM, et al. Phase I trial of docetaxel and vinorelbine in patients with advanced nonsmall cell lung carcinoma. Cancer. 2000; 88:1045–1050. [PubMed: 10699893]
12. Georgoulias V, Papadakis E, Alexopoulos A, et al. Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. Lancet. 2001; 357:1478–1484. [PubMed: 11377599]
13. Kosmidis P, Mylonakis N, Nicolaides C, et al. Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol. 2002; 20:3578–3585. [PubMed: 12202657]
14. Kosmidis PA, Kalofonos HP, Christodoulou C, et al. Paclitaxel and gemcitabine versus carboplatin and gemcitabine in patients with advanced non-small-cell lung cancer. A phase III study of the Hellenic Cooperative Oncology Group. Ann Oncol. 2008; 19:115–122. [PubMed: 17938425]

Table 1

Patient Characteristics (N=25)

Characteristic	No. (%)
Median age, yr (range)	64 (50–81)
Women	11 (44%)
Tobacco	
Current	3 (12%)
Former	17 (68%)
Never (<100 cigarettes)	5 (20%)
KPS	
90	17 (68%)
80	7 (28%)
70	1 (4%)
Surgical Procedure	
Wedge Resection	4 (16%)
Lobectomy	19 (76%)
Bilobectomy	2 (8%)
Pathologic Stage	
IB	7 (28%)
IIA	3 (12%)
IIB	7 (28%)
IIIA	7 (28%)
IIIB	1 (4%)
Histology	
Adenocarcinoma	21 (84%)
Squamous cell carcinoma	4 (16%)
Days Surgery to 1st chemotherapy median, (range)	58 (43–97)

Table 2

Comparison of drug delivery and toxicity in published phase II-III studies of adjuvant chemotherapy (vinorelbine plus docetaxel, cisplatin plus vinorelbine, cisplatin plus docetaxel)

	Cisplatin %		Vinorelbine %		Docetaxel %		Grade 3/4 hematologic toxicity (%)	Grade 3/4 non-heme toxicity (%)
	4 cycles	Dose intensity	4 cycles	Dose intensity	4 cycles	Dose intensity		
vin+doce	NA	NA	60	88	56	84 (60 mg/m^2) 78 (45 mg/m^2)	64	52
JBR.10[7]	50	84	50	52	NA	NA	73	15 fatigue 17 n/v 8 infection
ANITA[4]	49	85	50	56	NA	NA	85	28 asthenia 27 n/v 20 infection
MSKCC cis+doce[8]	44	75	NA	NA	NR	NR	15	44

abbreviations: n/v (nausea and/or vomiting); NA (not applicable), NR (not reported); vin (vinorelbine); doce (docetaxel); cis (cisplatin)