The Feasibility of Adjuvant Carboplatin and Docetaxel in Patients with Curatively Resected Non-small Cell Lung Cancer

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Introduction: Adjuvant cisplatin-based chemotherapy improves overall survival; however, chemotherapy compliance has been difficult. Carboplatin (C) is better tolerated than cisplatin, and carboplatin-based adjuvant therapy may have better chemotherapy compliance.

Methods: The primary end point of this multicenter phase II trial was the feasibility of delivering carboplatin and docetaxel (C/D). An "adequate exposure" was defined as receiving four cycles of C/D within 12 weeks of initiating adjuvant therapy. A sample size of 72 patients provided 88% power to detect a true adequate exposure of rate of at least 80%. Patients with resected non-small cell lung cancer, a good functional status, and preserved organ function were eligible. Adjuvant therapy was initiated between 2 and 8 weeks after surgery, and consisted of four cycles C (area under the curve = 6), and D 75 mg/m^2 every 3 weeks.

Results: Seventy-two patients were treated, and the patient demographics were: median age 65 years (range 47–84), gender male/female 67%/33%, stage I (40%), II (36%) IIIA (22%) and IIIB (1%), and the two most common histologies were: adenocarinoma (44%), and squamous cell carcinoma (42%). Fifty-seven patients (79%) received four cycles within 12 weeks, and 15 (21%) of patients did not complete four cycles for the following reasons: adverse events (n = 5), patient refusal (n = 5), disease progression during active therapy (n = 3), and intercurrent illness (n = 2). No treatment related deaths were observed and the primary toxicities were hematologic (grade 4 neutropenia 42% and febrile neutropenia 11% of patients). Twenty-six patients (36%) received growth colony stimulating factor (G-CSF) supportive therapy during their treatment, and G-CSF supportive therapy was used in 21.6% of all cycles.

Conclusions: C/D has an acceptable toxicity profile with the use of G-CSF supportive therapy and the majority of patients completed four cycles of therapy within 12 weeks.

Key Words: Adjuvant chemotherapy, Chemotherapy compliance, Treatment compliance, Non-small cell lung cancer, Carboplatin, Docetaxel.

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Lung cancer is the leading cause of cancer death in the United States, and it is estimated that in 2007, more patients will die of lung cancer than prostate, colon, and breast cancer combined.[1] Non-small cell lung cancer (NSCLC) histology is responsible for about 85% of the cases, and approximately 45% of patients will present with stage I–IIIA disease.[2,3] Surgical resection remains the standard of care of patients with stage I–II disease, and a subset of patients with stage IIIA disease. Despite complete surgical resection recurrence rates are high with the majority of the recurrences being distant metastases. In 1995, the NSCLC Collaborative Group reported a meta-analysis that evaluated the efficacy of cisplatin-based adjuvant chemotherapy in resected NSCLC.[4] This meta-analysis revealed an absolute survival benefit of 5% which approached, but did not reach absolute statistical significance (hazard ratio [HR] = 0.87, p = 0.08). These provocative results led to the development of at least five randomized controlled trials evaluating the efficacy of cisplatin-based chemotherapy[5–9]; three of these trials have revealed an improvement in overall survival with adjuvant cisplatin-based therapy.[5–7] The recent lung adjuvant cisplatin evaluation (LACE) meta-analysis of the individual patient data from these five trials revealed a significant improvement in overall survival with the combination of cisplatin-based chemotherapy and surgery when compared with surgery alone (HR = 0.89, 95% confidence interval [CI] 0.82, 0.96; p = 0.004).[10] These trials and the meta-analysis have established the efficacy of adjuvant cisplatin-based therapy.

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TABLE 1. Chemotherapy Compliance on Recent Cisplatin-Based Adjuvant Trials [5–9]

Trial	*N*	Chemotherapy	No. of Cycles	Chemotherapy Compliance
ALPI	1209	MVP	3	69%[a]
IALT	1867	Cisplatin-based[b]	3 or 4	74%[c]
JBR.10	482	Cisplatin/vinorelbine	4	50%[d]
ANITA	840	Cisplatin/vinorelbine	4	Cisplatin 76%, vinorelbine 56%
BLT	381	Cisplatin-based[e]	3	60%[f]

[a] Fifty-one percent of patients who completed the MVP treatment had some dose adjustment or omission of the planned treatment.

[b] Treatment was required to be cisplatin-based (80 mg/m^2 for 4 cycles, 100 mg/m^2 for 3–4 cycles, or 120 mg/m^2 for 3 cycles). The most frequently used regimens were (% of patients receiving treatment): cisplatin/etoposide (49%) and cisplatin/vinorelbine (27%).

[c] Percentage of patients received at least a cumulative dose of 240 mg/m^2 of cisplatin.

[d] Percentage of patients completing 4 cycles of therapy after an amendment reducing the dosage of vinorelbine from 30 mg/m^2/weekly to 25 mg/m^2/weekly.

[e] Patients received one of 4 regimens (% of patents receiving treatment): cisplatin, mitomycin, vinblastine (42%), cisplatin, mitomycin, ifosfamide (33%), cisplatin, vindesine (3%), and cisplatin, vinorelbine (22%).

[f] Sixty percent of patients received all 3 cycles without a dose reduction of >10% or a delay of >7 days. Ten percent of patients had a dose reduction, 21% had a dose delay, and 7% had both.

ALPI, Adjuvant Lung Project Italy; MVP, mitomycin C, vindesine, cisplatin; ANITA, Adjuvant Navelbine International Trialist Association, JBR.10 National Cancer Institute of Canada JBR.10 trial; BLT, Big Lung Trial.

Eradication of micrometastatic disease requires an adequate exposure to adjuvant chemotherapy. The successful delivery of the intended three to four cycles of cisplatin-based chemotherapy in post-thoracatomy patients has been difficult; chemotherapy compliance rates have been between 50 and 75% (Table 1). The most common toxicities have been gastrointestinal (nausea and vomiting) and myelosuppression, and the rate of treatment-related deaths have been 1 to 2%. Chemotherapy compliance with cisplatin-based therapy outside the context of a clinical trial may be lower, and the treatment-related toxicity and mortality may be higher.

Two recent meta-analyses which compared cisplatin and carboplatin-based therapy for advanced NSCLC revealed a higher rate of ≥ grade 3 nausea and vomiting for cisplatin-based therapy.[11,12] In one meta-analysis there was 1.4-fold increase in treatment-related death in patients treated with cisplatin-based versus carboplatin-based therapy (3.9% versus 2.9%, respectively) which was not statistically significant (odds ratio = 1.36; 95% CI 0.89–2.07).[11] Cisplatin-based chemotherapy produced a higher response rate, but no significant improvement in survival when compared with carboplatin-based therapy.[11,12] In the palliative treatment setting, the increase in efficacy must be balanced with the increased toxicity of cisplatin-based therapy. However, in the adjuvant treatment setting a lower rate of toxicity, in a patient population susceptible to toxicity, may result in increased chemotherapy compliance and consequently an improvement in overall survival. Carboplatin and docetaxel is a standard therapy for advanced NSCLC with an acceptable toxicity profile.[13,14] At the time this trial was designed data on the feasibility of delivering carboplatin and docetaxel in the adjuvant setting were not available. Thus, we developed a multicenter phase II trial designed to investigate the feasibility of delivering four cycles of adjuvant carboplatin and docetaxel within a 12-week period.

During the time this trial was being conducted an interim analysis of Cancer and Leukemia Group B (CALGB) trial 9633 revealed a survival benefit of adjuvant carboplatin and paclitaxel when compared with observation in patients with stage IB NSCLC.[15] A subsequent interim analysis revealed a statistically significant difference in disease-free survival (HR = 0.74; 95% CI 0.57–0.96, $p = 0.03$), but no difference in overall survival (HR = 0.80; 95% CI 60–1.07, $p = 0.10$).[16] It is unclear whether the lack of a survival benefit seen was related to the relatively small size of the trial ($n = 344$) in a patient population with a lower risk of relapse, due to the use of carboplatin-based therapy, or potentially a true lack of overall survival benefit for adjuvant carboplatin-based therapy in patients with stage IB disease. The LACE meta-analysis of patients with stage IB disease ($n = 1371$) revealed a trend toward improved survival with adjuvant cisplatin-based therapy for patients (HR = 0.92, 95% CI 0.78–1.10).[10] The Japan Lung Cancer Research Group demonstrated an improvement in overall survival in patients with pathologically stage I disease treated with a nonplatinum-based treatment, uracil-tegafur, when compared with observation (HR = 0.71; 95% CI 0.52–0.98, $p = 0.04$).[17]

PATIENTS AND METHODS

Patient Eligibility

Patients were required to have undergone curative resection for stage I-IIIA NSCLC, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤1, age ≥18 years, adequate renal function (defined as a serum creatinine within upper limit of normal (ULN) or a calculated creatinine clearance of ≥40 ml/min), total bilirubin within ULN, and adequate bone marrow function (defined as an absolute neutrophil count of 1500/mm^3, hemoglobin ≥8 g/dl, and platelets ≥100,000/mm^3). Patients with elevated alkaline phosphatase (AP) between 1 and ≤2.5 X ULN were eligible if the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were ≤1.5 X ULN. Patients with AP between >2.5 and ≤5 X ULN were eligible if the AST or ALT were within ULN. Patients with a history of a previous malignancy were eligible if the attending oncologist believed that adjuvant chemotherapy was indicated and potentially beneficial to the patient. Patients with an AP, AST, or ALT ≥5 X ULN, women currently breast-feeding, patients with a history of severe hypersensitivity to docetaxel or polysorbate 80, and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 baseline neuropathy grade ≥2 were not eligible. Patients signed informed consent before any study related tests being performed. All patients who met the eligibility criteria were offered participation in this clinical trial. This protocol was reviewed by the protocol review committee of Lineberger Comprehensive Cancer Center, and the Institutional Review Board of the participating institutions. The investigators were required to comply with good clinical practice and the principles that have their origin in the Declaration of Helsinki.

TABLE 2. Carboplatin and Docetaxel Dose Modifications for Toxicity

Dose Level	Docetaxel Dose (mg/m^2)	Carboplatin Dose (AUC)
0	75	6
−1	60	6
−2	60	5
−3	50	5

AUC, area under the curve.

Treatment

Patients were required to initiate adjuvant therapy between 2 and 8 weeks after surgery. Chemotherapy treatment consisted of carboplatin area under the curve (AUC) of 6 using the Calvert equation[18] and docetaxel 75 mg/m^2 every 21 days for four cycles. Patients received dexamethasone 4 mg twice a day for 3 days starting 24 hours before the docetaxel administration. Standard antiemetics therapy was used, and the selection of the antiemetic agents was at the discretion of the treating physician. Patients were required to have an absolute neutrophil count $\geq 1500/mm^3$ and platelet count of $\geq 100{,}000/mm^3$ before initiating subsequent chemotherapy treatments. Patients experiencing a treatment delay of >2 weeks for any toxicity were taken off the trial. Chemotherapy doses were modified one dose level for afebrile grade 4 neutropenia ≥7 days, grade 4 neutropenia, associated with a fever, and grade ≥3 nonhematologic (Table 2). Patients experiencing grade 4 thrombocytopenia had both drugs reduce one dose level (i.e., carboplatin AUC = 5, and docetaxel 60 mg/m^2), and for a second occurrence of grade 4 thrombocytopenia the carboplatin dose was reduced to an AUC = 4, and the docetaxel remained 60 mg/m^2. Docetaxel was withheld for patients with a total bilirubin > ULN until total bilirubin ≤ ULN (for a maximum of 14 days). Docetaxel was withheld for elevated AP, AST, ALT >5 X ULN until the liver enzymes recovered (defined as having liver enzymes that met the eligibility criteria). Patients with persistently elevated liver enzymes underwent a dose reduction. The docetaxel dose was reduced one dose level for patients experiencing NCI CTCAE grade 2 neuropathy, and treatment was discontinued for patients experiencing grade 3 or 4 neuropathy. If stomatitis was present on day 1 of any cycle treatment was withheld until stomatitis resolved. The docetaxel dose was reduced one dose level for grade 3 or 4 stomatitis. The protocol recommended that treating physician follow the American Society of Clinical Oncology (ASCO) guidelines for the use of growth colony stimulating factors (G-CSF) and red blood cell growth factors that were available at the time the protocol was being performed.[19,20]

Study Design and Statistical Analysis

This trial was a multicenter, single-arm phase II trial and the primary objective was to evaluate the feasibility of delivering carboplatin and docetaxel. An "adequate exposure" was defined as a patient receiving four cycles of adjuvant therapy within 12 weeks of initiating the first dose. Taking the "null hypothesis" rate of 65% "adequate exposure," a sample of 72 evaluable patients was required to have a 88% power to detect a true "adequate exposure" rate of 80%, using a one-sided χ^2 test. The secondary objectives were to describe the toxicity associated with adjuvant carboplatin and docetaxel, to assess the patterns of recurrence and survival after adjuvant carboplatin and docetaxel. The toxicity was assessed by the treating physician after each cycle using the NCI CTCAE version 3.0.

The Kaplan-Meier (or product limit) method was used to estimate the time to event functions of relapse free survival and overall survival. Relapse free survival has been defined as the time between the date of the start of treatment to disease progression or death (which ever occurs first) or the date of last contact. Overall survival has been defined as the time from the date of the start of treatment to the date of death or the date of last contact. The log-rank test was used to test for the possible differences between estimated the time to event curves. Statistical analyses were performed with SAS statistical software, versions 9.1, SAS Institute Inc., Cary, NC.

RESULTS

Patients

From June 2004 to December 2006, 75 patients were enrolled on the trial. Three patients withdrew consent before initiating therapy, and data on the 72 patients who were enrolled and received treatment on the trial is included in the patient demographics, and the toxicity and feasibility analysis. The majority of the patient were white (83%), and had a PS of 0 to 1 (99%) (Table 3). The two most common histologies were adenocarcinoma and squamous cell carcinoma (44% and 42%, respectively), and the majority of the patients had stage I or II disease (76%). One patient with stage IIIB (T4N0M0) with a T4 status (based on two malignant nodules within the same lobe of the lung) was allowed to enroll on the protocol after an Institutional Review Board exemption was obtained. One patient with a PS of 2 was enrolled on the protocol and received four cycles of therapy. Only 15% of patients had undergone pneumonectomy.

Treatment Administration

Of the 72 patients enrolled and treated on the trial, 57 (79%) received four cycles of therapy within 12 weeks (Table 4). A total of 15 patients (21%) did not complete four cycles of therapy. The reasons for discontinuing therapy were: adverse events ($n = 5$), patient refusal ($n = 5$), disease progression during active therapy ($n = 3$; abdominal mass ($n = 1$), and brain metastases ($n = 2$)), intercurrent illness ($n = 2$)). Twelve patients (17%) had the docetaxel dose reduced for a total of 21 cycles. The reasons for dose reduction were: afebrile grade 4 neutropenia ≥7 days ($n = 6$), febrile neutropenia ($n = 4$), grade 3 diarrhea ($n = 1$), and grade 3 dehydration ($n = 1$). Eleven of the 12 patients who underwent dose reduction completed four cycles of therapy; five patients had cycle 4, three patients had cycles 3 and 4, and three patients had the cycles 2, 3, and 4 dose reduced. One patient underwent one additional cycle of therapy after dose reduction then discontinued therapy. The number of

TABLE 3. Patient Demographics ($N = 72$)

Parameter	
Median age	65 yr (range 47–84 yr)
Ethnicity	
White	83% ($n = 60$)
African American	10% ($n = 7$)
Latino	3% ($n = 2$)
Asian	1% ($n = 1$)
Gender (female/male)	33%/67%
Performance status	
0	39% ($n = 28$)
1	60% ($n = 43$)
2	1% ($n = 1$)
Stage	
I	40% ($n = 29$)
T1N0	8% ($n = 6$)
T2N0	32% ($n = 23$)
II	36% ($n = 26$)
T1N1	12.5% ($n = 9$)
T3N0	3% ($n = 2$)
T2N1	21% ($n = 15$)
IIIA	22% ($n = 16$)
T3N1	3% ($n = 2$)
T1N2	4% ($n = 3$)
T2N2	12.5% ($n = 9$)
T3N2	3% ($n = 2$)
IIIB	
T4N0	1% ($n = 1$)
Histology	
Adenocarcinoma	44% ($n = 32$)
Squamous cell carcinoma	42% ($n = 30$)
Non-small cell—not otherwise specified	10% ($n = 7$)
Large cell carcinoma	4% ($n = 3$)
Type of surgery	
Wedge resection	3% ($n = 2$)
Lobectomy	72% ($n = 52$)
Bi-lobectomy	10% ($n = 7$)
Pneumonectomy	15% ($n = 11$)

TABLE 4. Chemotherapy Compliance

Parameter	Percentage (n)
Completed chemotherapy within 12 wk	79 (57)
Dose	74 (53)
After dose reduction	5.5 (4)
Reasons for treatment discontinuation	
Adverse events	7 (5)
Patient refusal	7 (5)
Disease progression	4 (3)
Inter-current illness	3 (2)

patients completing therapy at the full dose within 12 weeks was 53 (74%). The dose intensity, defined as dose patients received/intended dose, for carboplatin and docetaxel was 87.5% and 86%, respectively.

TABLE 5. Treatment-Related Toxicity[a] ($N = 72$)

	Grade 3 (%)	Grade 4 (%)	Grade 3/4 (%)
Hematologic toxicity			
Neutropenia	24	42	65
Thrombocytopenia	1		1
Febrile neutropenia	3	8	11
Non-hematologic toxicity			
Gastointestinal			
Nausea	1		1
Vomiting	1		1
Diarrhea	3		3
Infusional reactions	4		4
Constutional			
Dehydration	1		1
Fatigue/asthenia	5.5		
Cardiac			
Syncope	5.5		5.5
Arrythmia[b]		1	1
Proteinuria		1	1
Infection		3	3
Dyspnea		1	1

[a] Worst grade of each individual toxicity reported.
[b] Supraventricular tachycardia.

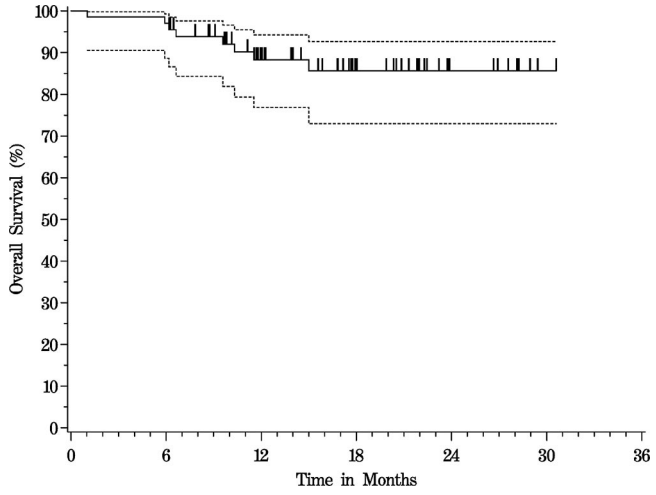

FIGURE 1. Overall survival.

Toxicity

The primary toxicity seen on this trial was neutropenia with 65% of patients developing grade 3 or 4 neutropenia (Table 5). Forty-two percent of patients developed grade 4 neutropenia and 11% experienced grade 3 or 4 febrile neutropenia. The rate of grade 3 or 4 anemia or thrombocytopenia was low; 0% and 1%, respectively. The rate of nonhematologic toxicities was low with the most frequent toxicities being fatigue/asthenia (5.5%), syncope (5.5%), and docetaxel infusion related reactions (4%). The use of G-CSF was not mandated in the protocol; however, 26 (36%) patients received G-CSF at some point during the treatment. Eleven

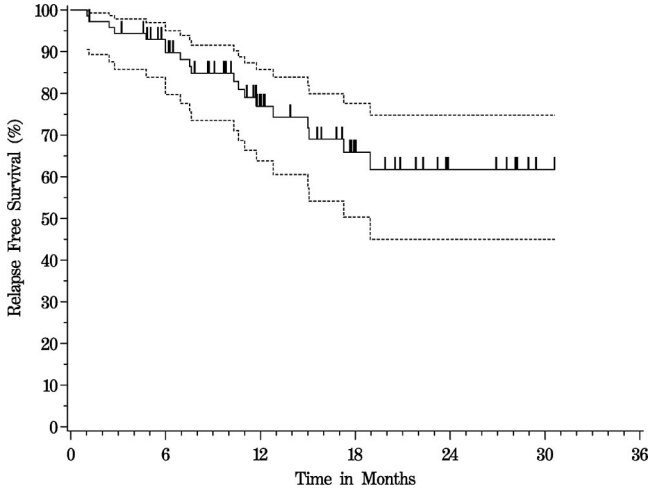

FIGURE 2. Relapse-free survival.

patients received G-CSF during the first cycle, and six patients received it during all four cycles. G-CSF supportive therapy was used with 54 (21.6%) cycles of therapy.

Survival

Of a total of 72 patients that had been followed for survival information, only eight have died and 64 were still alive at the time of analysis (Figure 1). The median follow-up time for survivors was almost 16 months (range 1–31 months). At the time of the analysis the median survival time had not been reached, and the overall survival rate at 18 months was 86% (95% CI: 73–93%). Twenty-two survivors were alive more than 18 months from the date of the start of treatment. Of the eight patients who have died, five had a documented relapsed before death. A total of 19 have either relapsed or died (Figure 2), and the relapse free survival at 18 months was 66% (95% CI: 50–78%). Of the patients who have experienced relapse, four patients have experienced intrathoracic relapse, five a combination of intrathoracic and distant relapse, and 10 patients distant relapse alone, of which eight were within the brain. The stage distribution of patients experiencing isolated brain relapse were: stage I ($n = 2$), stage II ($n = 2$), and stage III ($n = 4$).

DISCUSSION

Although the rate of chemotherapy compliance did not exactly reach the definition of "adequate exposure" of 80% of patients receiving for cycles within a 12-week treatment period, 79% of our patients did complete the treatment with 12 weeks, and 74% completed four cycles at full dose within 12 weeks. The definition of adequate exposure and four treatment cycles was selected based on the fact that adjuvant cisplatin-based trials have used four cycles of adjuvant therapy[5–7] was based on testing the hypothesis that compliance with adjuvant carboplatin-based therapy would be superior to compliance of cisplatin-based therapy seen on previous trials. The number of cycles and the compliance rate has not been associated with the efficacy of adjuvant therapy, and thus the selection of this values was arbitrary. The fact that patients had to receive the four treatments with 12 weeks (or day 84 after the initiation of chemotherapy) provides accommodation for dose delays related to treatment related complications or medical illnesses as well; however, if any single cycle was delayed for >2 weeks the patient was taken off trial. For example, a patient could receive his four treatments at 4 weeks intervals (i.e., receive cycles 1–4 on days 1, 28, 56, and 84, respectively) and still meet the predefined criteria of completing all four cycles within 12 weeks of receiving the first treatment.

The chemotherapy compliance seen on this trial was similar to CALGB 9633 which investigated adjuvant chemotherapy with the combination of carboplatin (AUC = 6) and paclitaxel 200 mg/m^2 every 3 weeks for four cycles over 12 weeks. Preliminary chemotherapy compliance data from CALGB 9633 ($n = 124$ patients) revealed 85% of patients received four cycles of therapy, and 55% received the four cycles at full dose.[15] Adverse event data is available on 158 patients on the CALGB 9633 trial, and grade 3 or 4 toxicities seen at a rate of ≥10% were neutropenia (35%) and hyperglycemia (15%).[16] No treatment related deaths were seen on CALGB 9633 or our trial.

The chemotherapy compliance seen on this trial compares favorably to the chemotherapy compliance seen on trials of cisplatin-based adjuvant therapy which has ranged from 50 to 75% of the intended dose (Table 1). A recent multicenter phase II trial investigated the feasibility of delivering four cycles of adjuvant cisplatin and docetaxel.[21] Two different docetaxel schedules were investigated, and the primary end point for this trial was the amount of cisplatin given over a planned four cycles of adjuvant therapy.[21] Patients on one cohort received docetaxel 35 mg/m^2 on days 1, 8, 15, and cisplatin 80 mg/m^2 on day 15 every 4 weeks, and patients on the second cohort received docetaxel 75 mg/m^2 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. This trial used a two-stage design, and if <12 of the first 16 (75%) patients tolerated more than three cycles of therapy the trial would be stopped. Sixteen patients were treated on the weekly docetaxel schedule and five of the 16 (31%) were unable to complete three cycles of therapy, and 11 patients were treated on the cohort with every 3 week docetaxel, and six of the first 11 (55%) were unable to complete three cycles, and in accordance with the trial design the trial was discontinued. Among the 11 patients who failed to complete three cycles of chemotherapy the primary reason was toxicity, and the main toxicities were one or more of the following: fatigue ($n = 8$), nausea ($n = 4$), febrile neutropenia ($n = 1$), hypotension ($n = 1$), and nephrotoxicity ($n = 1$). The fact that chemotherapy compliance was problematic in both cohorts is suggestive that the cisplatin is the primary agent responsible for the observed toxicity. The intolerance of the cisplatin and docetaxel combination is in contrast to the acceptable toxicity and chemotherapy compliance of the carboplatin and docetaxel combination seen on our trial.

A multivariate analysis of chemotherapy compliance of patients treated on the JBR.10 trial revealed factors associated with chemotherapy compliance were extent of surgery, gender, age, and patient's treatment country.[22] Patients randomized in Canada were less likely to complete chemotherapy due to patient refusal than their American counterparts.

The current trial was performed entirely in the United States, and was performed after trials revealing the benefits of adjuvant chemotherapy had been published or presented. This may have influenced patients and physicians willingness to tolerate toxicity, and contributed to rate of chemotherapy compliance observed on this trial. All patients who met the eligibility criteria were offered the option of participation in the clinical trial which is our standard practice policy. This policy reduces the influence of patient selection bias for our clinical trials; however, subtle forms of physician and patient selection bias may have influenced enrollment in the trial and chemotherapy compliance. The fact that patients were treated on a clinical trial with the specific goal of completing four cycles of therapy within a 12-week period may influenced physicians treatment decisions and increased chemotherapy compliance as well.

On JBR.10 patients who underwent pneumonectomy were more likely to discontinue therapy because of toxicity than patients with lesser resections. The percentage of patients undergoing pneumonectomy was comparable between the two trials; 54 patients (25%) on JBR.10 and 11 patients (15%) on our trial. Nine of the 11 patients who underwent pneumonectomy completed four cycles of therapy; two patients did not complete therapy due to disease progression. Female patients were also less likely to complete chemotherapy on JBR.10 as well. The percentage female patients receiving adjuvant therapy on JBR.10 was similar to our trial (36% versus 33%, respectively). Nineteen of the 24 (79%) female patients on our trial completed four cycles of therapy.

A retrospective analysis of elderly patients (defined as age >65 years) on the JBR.10 trial revealed that adjuvant therapy provided a survival benefit for elderly patients (HR = 0.61; 95% CI 0.38–0.98; $p = 0.04$).[23] However, fewer elderly patients completed treatment and more refused treatment ($p = 0.03$).[23] None of the elderly patients received the full 16 dose of vinorelbine and only 32% received the intended eight doses of cisplatin. This data is suggestive that even with a reduced dose delivery of adjuvant chemotherapy that there is a survival benefit to treatment and that chemotherapy compliance in the elderly may be a significant challenge. Sixty-three of the 213 patients (30%) who received adjuvant chemotherapy on JBR.10 were age >65. The median age of patients on our trial was 65 years, and 16 patients (22%) were aged ≥70 years. Twenty-five of the 33 (76%) patients who were aged >65 years completed four cycles of therapy.

The chemotherapy compliance and toxicity seen with this adjuvant carboplatin and docetaxel on this trial was similar to carboplatin and docetaxel in the advanced disease setting. A randomized phase III trial of carboplatin and docetaxel in the advanced disease of Fossella et al. revealed that the median number of cycle of carboplatin and docetaxel patients received was six, and the relative dose intensity was 93%.[13] The percentage of patients experiencing febrile neutropenia and grade 3/4 neutropenia was 4.5% and 74.4%, respectively. The percentage of patients experiencing of grade 3 or 4 nonhematologic toxicities on the trial by Fossella et al. were: (asthenia (10.7%), diarrhea (5.2%), infection (11%), and pulmonary (13.5%). In a phase II trial by Belani et al. 85% of patients experienced grade 3/4 neutropenia and 15% experienced febrile neutropenia.[14] The most common nonhematologic toxicity seen was asthenia (24% of patients).

It should be noted that the ASCO recommendations for the use of G-CSF's have recently been revised, and the guidelines recommend primary prophylaxis for the prevention of febrile neutropenia in patients who are at high risk based on age, medical history, disease characteristics, and degree and frequency of myelosuppression of the chemotherapy regimen.[24] The current ASCO guidelines recommend that G-CSF be used when the risk of febrile neutropenia is approximately 20%. The National Comprehensive Cancer network (NCCN) guidelines currently consider the combination of carboplatin and docetaxel to be a high risk (defined as ≥20% risk for febrile neutropenia) regimen and recommend the prophylactic use of G-CSF.[25] The use of primary prophylaxis for febrile neutropenia with G-CSF was not mandated in this trial; however, the use of G-CSF in 36% of the patients significantly reduced the rate of grade 3 or 4 neutropenia and febrile neutropenia, and contributed to the rate of chemotherapy compliance on this trial. The use of primary prophylaxis with G-CSF with all cycles of therapy may further reduce the toxicity, the number of dose reductions, and improvement chemotherapy compliance further.

The relative efficacy and toxicity of carboplatin and cisplatin in advanced stage disease has frequently been debated, and two recent meta-analyses have investigated this issue. A meta-analysis by Hotta et al. revealed a statistically significant survival advantage for cisplatin in combination with third-generation regimens when compared with carboplatin in combination with third-generation regimens (HR = 1.106, 95% CI = 1.005–1.218; $p = 0.039$).[11] A separate meta-analysis using individual patient data revealed that in patients treated with platinum in combination with third-generation agents, patients receiving cisplatin had a superior survival when compared with patients receiving carboplatin.[12] These differences in carboplatin and cisplatin efficacy may have limited clinical implications in the palliative setting, but significant clinical implications when treating in the curative setting. However, a more active regimen that cannot be delivered due to toxicity in the patient population of interest may erode its advantage over less active regimens. Certainly cisplatin-based therapy should be considered the standard given the results of recent phase III trials and the LACE meta-analysis. However, many patients are not optimal candidates for cisplatin-based therapy or may experience excessive toxicity. Although carboplatin-based chemotherapy should be considered investigational we believe it remains an option for patients who can not tolerate cisplatin-based therapy. We believe the issue of the optimal choice of platinum agents (cisplatin versus carboplatin) in the adjuvant setting is worthy of a phase III trial. The upcoming ECOG adjuvant trial, ECOG 1505, will evaluate the efficacy of cisplatin-based chemotherapy with and without bevacizumab, and the three chemotherapy combinations that will be used will be cisplatin/vinorelbine, cisplatin/docetaxel, and cisplatin/gemcitabine.[26] This trial should provide valuable information

about the potential efficacy of bevacizumab and third generation cisplatin combinations in the adjuvant setting.

CONCLUSION

In conclusion, the combination of carboplatin and docetaxel has an acceptable toxicity profile with the use of G-CSF supportive therapy in the adjuvant setting, and the primary toxicities are hematologic. The majority of patients completed the four cycles of therapy within 12 weeks. We believe that adjuvant therapy with carboplatin and docetaxel in patients who have contraindications to cisplatin or patient populations with poor chemotherapy compliance is a reasonable alternative.

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