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Scientific Research

Feasibility Study for Biweekly Administration of Cisplatin plus Vinorelbine as Adjuvant-Chemotherapy for Completely Resected Non-Small Cell Lung Cancer Patients in a Japanese Population

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Abstract

Purpose: To evaluate the feasibility of biweekly administration of cisplatin and vinorelbine as adjuvant chemotherapy for patients with completely resected non-small cell lung cancer (NSCLC). Patients and Methods: This was a single-arm, single-institutional study. Patients with completely resected NSCLC (p-Stage IB-IIIA) with no previous chemotherapy or radiotherapy were eligible. Simon's optimal two-stage design was applied. Both cisplatin (50 mg/m^2) and vinorelbine (25 mg/m^2) were given on days 1 and 15, every 28 days. The primary endpoint of this study was the feasibility of this combination in the four cycles of treatment. Results: Twenty patients (19 lobectomies and 1 pneumonectomy) were enrolled in this study. 10 (50%) of patients had grade 3/4 neutropenia, and 3 (15%) had grade 3/4 anemia. Severe non-hematologic toxicities were uncommon in this series. No treatment-related death was encountered. 18 (90%) patients completed the planned 4 cycles of chemotherapy. The median intensity was 24.3 (range 18.1 to 25) mg/m^2/week with an average of 23.6 (21 - 25) mg/m^2/week cisplatin and 12.5 (range 10 to 12.5) mg/m^2/week with an average of 12.3 (10 - 12.5) mg/m^2/week vinorelbine. The median relative dose intensity of cisplatin was 97.5% (range 72.5% to 100%) with an average of 94.6% (72.5% - 100%) and that of vinorelbine was 100% (range 80% to 100%) with an average of 97.8% (80% - 100%). Conclusion: This regimen is feasible in the treatment of patients with completely resected NSCLC. A phase III trial

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is warranted to assess the efficacy of this regimen at promoting survival and preventing recurrence.

Keywords

NSCLC; Adjuvant Chemotherapy; Cisplatin and Vinorelbine; Biweekly

1. Introduction

Lung cancer is the leading cause of cancer mortality in Japan and 60,000 people or more a year died of lung cancer. In addition, the number of people that die of lung cancer increases every year. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers [1] [2]. Despite progress in imaging and diagnostic procedures, patients with NSCLC are still found in advanced conditions and only about 30% show an early resectable stage at the time of diagnosis [2]. The radical treatment for clinical stages IA-IIB and part of IIIA NSCLC is a surgical resection. However, the recurrence occurs in 36% to 71% of patients who are treated by surgical resection [3]-[6]. Therefore, they have been considered to be caused by micrometastatic lesions already present at the time of the surgical resection.

There have been some attempts to administer postoperative adjuvant chemotherapy to selected patients of NSCLC with the aim of reducing the mortality associated with postoperative recurrence. But, before 2000, most clinical studies on postoperative adjuvant chemotherapy have failed to demonstrate its usefulness for survival [7]-[10]. After 2000, to improve the post-operative survival of NSCLC patients, several randomized phase III trials have been conducted to determine the benefit of adjuvant chemotherapy over surgery alone [11]-[14], as follows: International Adjuvant Lung Cancer Trial (IALT) based on cisplatin [11]; JBR 10 trial by the combined use of cisplatin plus vinorelbine; Adjuvant Navelbine International Trialist Association (ANITA) trial by the combined use of cisplatin and vinorelbine [12] [14]. IALT reported there was a statistically significant advantage in overall survival of 4.1% at 5 years in favor of adjuvant chemotherapy [11]. JBR 10 trial showed that cisplatin plus vinorelbine improved the 5-year survival rate by 15% in patients with pathological stage IB to IIB NSCLC [14]. ANITA trial showed that cisplatin plus vinorelbine improved the 5-year survival rate by 8.6% in patients with pathological stage IB to IIIA NSCLC [12]. These positive results have changed the therapeutic strategy for resectable NSCLC. The Lung Adjuvant Cisplatin Evaluation (LACE) study, which was based on a pooled meta-analysis [15], indicated that adjuvant cisplatin-based chemotherapy could improve survival in patients with completely resected NSCLC, especially in p-Stages II and III. Thus now cisplatin-based regimens, particularly cisplatin plus vinorelbine, have been recommended as postoperative adjuvant chemotherapy for NSCLC [16].

Although the optimal dose of cisplatin has been controversial, LACE [15] reported a favorable prognosis in a subset analysis in their study with patients who received more than 300 mg of cisplatin. However, in these positive previous studies, it was poor compliance that the total dose of the cisplatin was less than 300 mg or the completing rate of all planned cycles was about 50%. In IALT, 73.8% of patients received at least 240 mg/m^2 of cisplatin in combination with vinblastine, vinorelbine or etoposide [11]. In JBR 10, 48% of patients in this series received 4 complete cycles of cisplatin [14] [17]. In ANITA [12], 49% of patients in this series received 4 complete cycles of cisplatin.

We previously showed biweekly administration of cisplatin plus gemcitabine for adjuvant chemotherapy in completely resected patients with p-Stage IB, II and IIIA NSCLC is good compliance compared with these positive studies [18]. Even after the operation, it is suggested that it is possible to do safely by biweekly administeration of cisplatin for adjuvant chemotherapy.

In addition, there is no report on the safety and compliance of biweekly administration of cisplatin and vinorelbine for adjuvant chemotherapy in Japanese patients. Under these circumstances, we undertook this study to investigate the safety and compliance of postoperative adjuvant chemotherapy with cisplatin (50 mg/m^2) and vinorelbine (25 mg/m^2) administered on days 1 and 15, every 28 days in Japanese patients with completely resected non-small cell lung cancer.

2. Patients and Methods

This was a single-arm, single-institutional study. The primary endpoint of this study was the feasibility of biweekly

administration of cisplatin plus vinorelbine as adjuvant chemotherapy in Japanese patients with curatively resected NSCLC, defined as the ratio of achieving treatment without unacceptable toxicity in the first four cycles of treatment. The secondary endpoint was the safety, which was assessed in terms of the frequency and degree of adverse events with this treatment.

2.1. Patient Eligibility

Patients who were completely resected with pathologically documented Stage IB-IIIA NSCLC were enrolled in this study. The eligibility criteria were no previous chemotherapy, radiotherapy, or immunotherapy, ECOG performance status 0 - 1, age between 20 - 75, adequate bone marrow functions (leukocyte cell count $\geq$4000/mm^3, neutrophil count $\geq$ 2000/mm^3, platelet count $\geq$ 10,000/mm^3 and hemoglobin $\geq$ 9.5 g/dl), and preserved liver function (total bilirubin $\leq$ 1.5 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) $\leq$ 2.5 times of normal value), renal function (serum creatinine $\leq$ 1.5 mg/dl,), and pulmonary function ($PaO_2 \geq 60$ Torr or $SpO_2 \geq 90\%$ in atmosphere pressure). Patients with concomitant malignancy, active infection or other serious medical problems were excluded. All patients were required to enroll in this study within 4 to 8 weeks after surgery. The local ethics committee approved this study, and written informed consent was obtained from all patients.

2.2. Study Design

Criteria were planned according to the Simon's optimal two-stage design [19]. was given at 25 mg/m^2 by infusion over 30 minutes, and followed by cisplatin, which was given at doses of 50 mg/m^2 by continuous infusion over 2 hours on day 1 and day 15 (Level 1) every 4 weeks. Patients were evaluated as follows. Toxicity was assessed before and at the middle of each cycle of chemotherapy, according to version 3.0 of the National Cancer Institute Common Toxicity Criteria. The minimum requirements to receive chemotherapy during the four cycles were as follows: absolute neutrophil count $\geq$2000/l, platelets $\geq$100,000/l, hemoglobin $\geq$8 g/dl and no grade $\geq$2 non-hematologic toxicity (excluding nausea, vomiting, anorexia, fatigue and alopecia). If these conditions were not met on days 1 and 15, chemotherapy was postponed or omitted, respectively, and dose reductions were planned: cisplatin 45 mg/m^2 and vinorelbine 25 mg/m^2 or the first stage, and cisplatin 45 mg/m^2 and vinorelbine 20 mg/m^2 for the second stage. If toxicity persisted after a two-week delay, treatment was stopped.

Antiemetic therapy consisted of 5-HT antagonist from days 1 to 3 and betamethasone 3 mg orally from days 1 to 5. G-CSF was administered if the patients showed first grade 4 and subsequent grade 3 neutropenia.

If 5 of the initial 7 patients who entered the protocol could not complete the planned treatment, the dose-levels were to be modified as follows: cisplatin 50 mg/m^2 and vinorelbine 20 mg/m^2 on days 1 and 15, 4qW (Level 2). If another 7 patients in Level 2 could not complete treatment, this protocol would be considered inadequate and terminated.

For toxicity analysis, the worst data for each patient across all cycles of chemotherapy were used. Unacceptable toxicities included febrile neutropenia, grade $\geq$ 3 neutropenia, thrombocytopenia and anemia, grade 4 emesis, grade $\geq$ 3 non-hematologic toxicity (other than hair loss), and any toxicity that worsened the general condition and made restaging impossible after four cycles.

2.3. Statistical Considerations

The primary outcome of this study was the feasibility of the combination, defined as the completion of four cycles of treatment without unacceptable toxicity. If the minimum acceptable rate and the hoped-for rate of patients who were able to complete the four cycles of treatment without unacceptable toxicity were set to 55% and 85%, respectively, type I and type II errors were both set equal to 0.10 and a power of 80%, 20 patients were required to conclude the study with a positive result. The relative dose intensity (RDI) was defined as the percentage of the expected dose administered to the patient (per unit of time expressed in mg/m^2/week).

3. Results

3.1. Patient Characteristics

From October 2008 to December 2009, 20 patients were enrolled in this trial. The baseline characteristics of the

patients are summarized in **Table 1**. The median age of the patients was 61.8 (range 38 to 75) years; 11 males and 9 females, and 20 were ECOG PS 0 upon entry. Nineteen (95%) patients underwent lobectomy and 1 (5%) underwent pneumonectomy. Two patients (10%) were p-Stage IB, one (5%) were p-Stage IIA, seven (35%) were p-Stage IIB and 10 (50%) were p-Stage IIIA. Patients were enrolled in this trial between 27 and 58 (median 35) days after surgery.

3.2. Toxicity

Both hematologic and non-hematologic toxicities are shown in **Table 2**. Neutropenia and anemia were the most common severe toxic effects of chemotherapy; 10 (50%) of patients had grade 3/4 neutropenia, and 3 (15%) had grade 3/4 anemia. Febrile neutropenia was not encountered and none of the patients required blood transfusion. Colony-stimulating factors were administered to 6 (30%) patients who had grade 4 neutropenia. Severe non-hematologic toxicities were uncommon in this series. Other toxicities were treated without events and did not disturb the planned treatment. No treatment-related death was encountered.

3.3. Compliance

A median number of 4 cycles were delivered (range 3 to 4), and 18 (90%) patients completed the planned 4 cycles of chemotherapy (**Table 3**). Two patients (10%) discontinued chemotherapy. The reasons for discontinuation was prolonged grade 2 serum creatinine elevation after the 4th cycle day 1, and patient's refusal after the 3rd cycle.

Nineteen (95%) patients received at least 300 mg/m^2 of cisplatin and 150 mg/m^2 of vinorelbine. The actuarial dose of cisplatin was a median of 390 (range 290 to 400) mg/m^2 with an average of 378.3 (range 290 to 400) mg/m^2, and that of vinorelbine was 200 (range 150 to 200) mg/m^2 with an average of 190.5 (range 150 to 200) mg/m^2; the dose intensity for cisplatin was 24.7 (range 23.1 to 25) mg/m^2/week (median) with an average of 24.2 (range 23.1 to 25) mg/m^2/week and that for vinorelbine was 12.5 (range 10 to 12.5) mg/m^2/week (median) with an average of 12.2 (range 10 to 12.5) mg/m^2/week. The median relative dose intensity of cisplatin was 97.5% with an average of 94.6%, and that of vinorelbine was 100% with an average of 95.3%.

Table 1. Baseline patient characteristics.

Characteristics	Number	%
Age, years		
Median	61.8	
Range	38 - 75	
Gender		
Male	11	55
Female	9	45
ECOG PS 0/1/2	20/0/0	100/0/0
Pathological stage		
IB	2	10
IIA	1	5
IIB	7	35
IIIA	10	50
Histological type		
Adenocarcinoma	16	80
Squamous cell carcinoma	4	20
Type of surgery		
Lobectomy	19	95
Pneumonectomy	1	5

Table 2. Worst toxicity according to NCI-CTC grade.

Toxicity	Toxicity Grade (CTCAE v3.0)							
	0 - 1		2		3		4	
	No. of Pt.	%	No. of Pt.	%	No. of Pt.	%	No. of Pt.	%
Leukopenia	5	25.0	10	50.0	5	25.0	0	0
Neutropenia	9	45.0	1	5.0	4	20.0	0	0
Thrombocytopenia	20	100.0	0	0	0	0	0	0
Anemia	6	30.0	11	55.0	3	15.0	0	0
Alb	19	95.0	1	5.0	0	0	0	0
AST	20	100.0	0	0	0	0	0	0
ALT	19	95.0	1	5.0	0	0	0	0
T-Bil	20	100.0	0	0	0	0	0	0
Creatinine	19	95.0	1	5.0	0	0	0	0
Hyponatoremia	19	95.0	1	5.0	0	0	0	0
Hyperkalemia	18	90.0	1	5.0	1	5.0	0	0
Hypercarcemia	20	100.0	0	0	0	0	0	0
γ-GTP	20	100.0	0	0	0	0	0	0
Nausea	20	100.0	0	0	0	0	0	0
Vomiting	20	100.0	0	0	0	0	0	0
Anorexia	20	100.0	0	0	0	0	0	0
Fatigue	20	100.0	0	0	0	0	0	0
Diarrhea	20	100.0	0	0	0	0	0	0
Constipation	20	100.0	0	0	0	0	0	0
Neuropathy: sensory	20	100.0	0	0	0	0	0	0
Anxiety	20	100.0	0	0	0	0	0	0
Phlebitis	20	100.0	0	0	0	0	0	0

Table 3. Chemotherapy compliance.

Patients who complieted cycles (% of treated patients)	
Cycle 1	20/20 (100%)
Cycle 2	20/20 (100%)
Cycle 3	20/20 (100%)
Cycle 4	18/20 (90%)

	CDDP	Vinorelbine
Planned cumulative dose (mg/m^2)	400	200
Actuarial cumulative dose (mg/m^2)		
Median	390 (290 - 400)	200 (150 - 200)
Average	378.3 (290 - 400)	190.5 (150 - 200)
Dose intensity [mg/(m^2 week)]		
Median	24.7 (23.1 - 25)	12.5 (10 - 12.5)
Average	24.2 (23.1 - 25)	12.2 (10 - 12.5)
Relative dose intensity (%)		
Median	97.5%	100%
Average	94.6%	95.3%

4. Discussion

To the best of our knowledge, this is the first report of a study designed to determine the feasibility of biweekly administration of cisplatin plus vinorelbine for adjuvant chemotherapy in completely resected patients with p-Stage IB, II and IIIA NSCLC.

After 2000, based on the information of The Non-small Cell Lung Cancer Collaborative Group that reported an improvement in the 5-year survival rate in the adjuvant chemotherapy group by 5% was observed as compared with that in the course observation group ($p = 0.08$) [20], several large phase III trials have been conducted to investigate the usefulness of postoperative adjuvant chemotherapy. The International Adjuvant Lung Cancer Trial Group (IALT) reported that there was a statistically significant advantage in overall survival of 4.1% at 5 years in favor of adjuvant chemotherapy of cisplatin in combination with vinblastine, vinorelbine or etoposide, among 1867 patients who were randomized after complete resection of p-Stage I-IIIA of NSCLC [11]. The National Cancer Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators (JBR 10) reported a 15% improvement in 5-year survival in the adjuvant chemotherapy arm in a total of 482 patients with pathological stage IB to IIB who were randomized to compare four cycles of cisplatin plus vinorelbine to an observation after complete resection of NSCLC [14]. The Adjuvant Navelbine International Trialist Association (ANITA) showed a 8.6% survival advantage at 5 years in an adjuvant chemotherapy group in a total of 840 patients with pathological stage IB to IIIA NSCLC who were randomized either to receive only observation or four cycles of chemotherapy with cisplatin plus vinorelbine [12]. On the other hand, the Cancer and Leukemia Group B (CALGB) 9633 trial showed that combined therapy with carboplatin and paclitaxel improved the 4-year survival rate by 12% in patients with pathological stage IB NSCLC [21]. A longer-term follow-up study, however, revealed no statistically significant improvement in the survival rate [22]. These studies showed that cisplatin-based adjuvant chemotherapy improves survival among patients who have undergone complete resection of NSCLC [11]-[15]. The Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group [15] reported a meta-analysis based on pooled individual patient data from the five largest randomized trials of adjuvant chemotherapy for NSCLC [8] [10]-[12] [14]. This meta-analysis revealed that the hazard ratio of death was 0.89 (95% C.I.; 0.82 - 0.96; $p < 0.005$), which corresponds to an absolute benefit in 5-year survival of 4.2% with chemotherapy, indicated that adjuvant cisplatin-based chemotherapy may improve survival in patients with completely resected p-Stage II and III NSCLC. Thus now cisplatin-based regimens, particularly cisplatin plus vinorelbine, have been recommended as postoperative adjuvant chemotherapy for NSCLC [16].

Although the optimal dose of cisplatin has been controversial, LACE [15] reported a favorable prognosis in a subset analysis in their study with patients who received more than 300 mg of cisplatin. However, in the previous positive phase III studies, it was poor compliance that the total dose of the cisplatin was less than 300 mg or the completing rate of all planned cycles was about 50%. IALT [11] settled on a range between 80 and 120 mg/m^2 per cycle of cisplatin and 73.8% of patients received at least 240 mg/m^2 of cisplatin in combination with vinblastine, vinorelbine or etoposide. In JBR 10, the planned total dose was 100 mg/m^2 per cycle for cisplatin and 100 mg/m^2 per cycle for vinorelbine for a total of 4 cycles, the median dose of cisplatin was 336 mg and 48% of patients in this series received 4 complete cycles of cisplatin [14] [17]. In ANITA [12], the planned doses of cisplatin and vinorelbine were 100 mg/m^2 per cycle and 120 mg/m^2 per cycle for a total of 4 cycles, the median dose of cisplatin was 304 mg and 49% of patients in this series received 4 complete cycles of cisplatin.

The combination of cisplatin plus vinorelbine has been reported to be an effective regimen for c-Stage IIIB-IV NSCLC in some phase III studies. The Four-Arm Cooperative Study in Japan also reported similar results with a comparison of cisplatin plus irinotecan as a reference arm to cisplatin plus gemcitabine, carboplatin plus paclitaxel, and cisplatin plus vinorelbine. In this trial, cisplatin plus vinorelbine showed a response rate of 33%, median survival time (MST) of 11.4 months and 2 year survival of 21%, and this difference was not statistically significant [23].

Especially for post-operative patients, the tolerability and adverse effects of chemotherapy, including myelotoxicity, should be considered. The biweekly administration of chemotherapy is becoming more accepted, since it makes it possible to maintain a similar dose intensity with a better toxic profile, especially with regard to hematologic toxicity, compared to a conventional administration schedule, such as on days 1, 8 and/or 15 every 3 or 4 weeks [24]. Previously We described the feasibility of biweekly administration of cisplatin plus gemcitabine for adjuvant chemotherapy in completely resected patients with p-Stage IB, II and IIIA NSCLC and

showed biweekly administration of cisplatin plus gemcitabine is safety and good compliance that the median dose of cisplatin was 346 mg and 65% of patients in this series received 4 complete cycles of cisplatin [18]. Under these circumstances, we undertook this study to investigate the safety and compliance of postoperative adjuvant chemotherapy with cisplatin (50 mg/m^2) and vinorelbine (25 mg/m^2) administered on days 1 and 15, every 28 days in Japanese patients with completely resected non-small cell lung cancer. In our series of patients, the planned dose was 100 mg/m^2 for cisplatin and 50 mg/m^2 for vinorelbine in one cycle for a total of 4 cycles; 19 (95%) patients received at least 300 mg/m^2 of cisplatin and 150 mg/m^2 of vinorelbine. The actuarial dose of cisplatin was a median of 390 (range 290 to 400) mg/m^2 with an average of 378.3 (range 290 to 400) mg/m^2, and that of vinorelbine was 200 (range 150 to 200) mg/m^2 with an average of 190.5 (range 150 to 200) mg/m^2. The median relative dose intensity of cisplatin was 97.5% with an average of 94.6%, and that of vinorelbine was 100% with an average of 95.3%, and 90% of the patients in this series received 4 cycles of treatment. Our treatment schedule could provide higher doses of cisplatin compared to trials that showed a survival advantage with adjuvant chemotherapy for completely resected NSCLC.

In this study, Neutropenia and anemia were the most common severe toxic effects of chemotherapy; 10 (50%) of patients had grade 3/4 neutropenia, and 3 (15%) had grade 3/4 anemia. Febrile neutropenia was not encountered and none of the patients required blood transfusion. Colony-stimulating factors were administered to 6 (30%) patient who had grade 4 neutropenia. Severe non-hematologic toxicities were uncommon in this series. Although nausea and anorexia of grade 3/4 was admitted by 27% and 15% in ANITA [12] and 10% and 10% was admitted in JBR-10 [14], it did not admit in this study at all. This was similar in Biweekly CDDP+GEM that we reported before [18]. In addition, we want to insist that neither nausea nor anorexia of grade 2 be admitted in this study. Other toxicities were treated without events and did not disturb the planned treatment. No treatment-related death was encountered. The proportion of treatment-related deaths is generally considered to be below 1.0%. Even if this proportion is low, the importance of treatment-related toxicity should be considered in the indications for adjuvant chemotherapy and in the discussion of adjuvant chemotherapy for patients with completely resected NSCLC.

5. Conclusion

In conclusion, our biweekly administration of cisplatin plus vinorelbine as adjuvant chemotherapy for completely resected p-Stage IB—IIIA NSCLC is feasible. Neutropenia and anemia should be carefully monitored. A phase III trial to assess the beneficial effects of this regimen on survival and the prevention of disease recurrence should be warranted.

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