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CLINICAL TRIAL/EXPERIMENTAL STUDY

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Evaluation of Safety and Efficacy of Salvage Therapy With Sunitinib, Docetaxel (Tyxan) and Cisplatinum Followed by Maintenance Vinorelbine for Unresectable/Metastatic Nonsmall Cell Lung Cancer

Stage 1 of a Simon 2 Stage Clinical Trial

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Abstract: Current chemotherapeutic regimens for nonsmall cell lung cancer (NSCLC) have reached a plateau over the last few years. Targeted therapy makes use of tyrosine kinase inhibitors (TKIs) to suppress a number of signaling pathways including epidermal growth factor receptor and vascular endothelial growth factor which are active in NSCLC biology. In this study, we used sunitinib, a multi-target receptor TKI, combined with chemotherapy for unresectable/metastatic NSCLC.

This open label Simon's 2 stage clinical trial enrolled a total of 6 NSCLC patients who received docetaxel (40 mg) and cisplatin (50 mg) on day 1 of each cycle (14 day interval between cycles) and sunitinib (25 mg qd for 10 days between cycles) for a total of 12 cycles (24 weeks), after which patients received maintenance therapy with vinorelbine (30 mg TIW) until disease progression. The sample size was based on a Simon's Optimal Two-Stage Designs for Phase II clinical trials. The expected response rate was set as 35% for P0 and as 60% for P1. The study was designed for a minimum of 6 patients for first stage and 15 patients until second stage with a significance level alpha = 0.10 and power = 70%. Diagnosis of a poor response in the second of 6 patients in Stage I or seventh of the 15 patients in Stage II would lead to early termination of the trial.

The overall response rate was 66.7%. Four patients had an overall survival >60 months. The time to PFS ranged from 3 to 42 months. The combination therapy was well-tolerated.

Sunitinib combined with chemotherapy shows promise and warrants further investigation.

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Abbreviations: CDD = continuous daily dosing, CNS = central nervous system, CR = complete response, EGFR = epidermal growth factor receptor, NSCLC = nonsmall cell lung cancer, OR = overall response, ORR = overall response rate, P0 = the probability of a poor response, P1 = the probability of a good response, PD = progressive disease, PFS = progression-free survival, PR = partial response, RTKI = receptor tyrosine kinase inhibitors, SD = sustained disease, Tkis = tyrosine kinase inhibitors, VEGF = vascular endothelial growth factor.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide.[1,2] Approximately 85% of lung cancers are classified as nonsmall cell lung cancer (NSCLC) and half of these patients present with advanced disease and unresectable tumors.[3] The prognosis of patients with advanced NSCLC treated with only chemotherapy, radiotherapy, or surgery was poor.[4] A number of strategies are being investigated to improve outcomes in these patients. Long-term survival data were recently reported for NSCLC patients with inoperable tumors who received combined chemotherapy and radiotherapy.[5] A study investigating predictors of good outcome showed that early N status (lymph node involvement), and surgery for initial therapy were significantly associated with long-term survival.[6] Platinum-based doublet chemotherapy which includes a taxane, gemcitabine, or vinorelbine is the current standard of care for patients with nononcogene-driven advanced/unresectable NSCLC, and is associated with 1-year survival rates of 30% to 40%.[7,8] Docetaxel/cisplatin-based neoadjuvant chemotherapy also

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showed promising results.[9] However, the heterogeneity in tumor genetics, and the mixed response to treatment at different tumor sites has resulted in a therapeutic plateau for most chemotherapy regimens at metastatic sites.

There has been a recent focus on understanding the molecular mechanisms by which targeted therapies inhibit specific pathways involved in tumorigenesis. The development of tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib as targeted therapy for NSCLC was based on the discovery that epidermal growth factor receptor (EGFR) signaling is a key event in NSCLC biology, and activating EGFR mutations were strong predictors of response to TKI therapy.[10] Cetuximab, an anti-EGFR monoclonal antibody, when used in combination with chemotherapy was shown to improve the response rate and overall survival in NSCLC patients.[11] However, the use of targeted therapies such as erlotinib and geftinib for NSCLC is limited by the fact that most patients who have EGFR activating mutations relapse after being treated with TKIs, and have a poor long-term prognosis.[12,13] Some data from randomized trials also showed no significant advantage when TKIs were combined with chemotherapy compared with chemotherapy alone.[14,15] It has been suggested that this could be because TKIs cause a G1 cell cycle arrest in lung cancer cell lines, thereby decreasing their sensitivity to cytotoxic agents.[16,17] Ongoing studies aim to evaluate sequential or intermittent regimens combining chemotherapy and TKIs in order to optimize efficacy.[18]

The recognition of angiogenesis as a key event in tumor progression led to the development of anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, which is used in combination with chemotherapy to treat specific populations of NSCLC patients.[19,20] However, some data suggested that patients with advanced/metastatic NSCLC treated with bevacizumab alone or in combination with chemotherapy had no significant improvement in overall survival (OS).[8] In contrast to single-target agents such as bevacizumab, multi-targeted receptor tyrosine kinase inhibitors (RTKI) such as sunitinib have been shown to inhibit a number of RTKs including VEGF receptors type 1 and 2, as well as platelet derived growth factor receptors.[21,22] Recent data from some clinical trials evaluating the safety and efficacy of sunitinib for advanced NSCLC showed promising results, with a response rate of 11.1%, and a median OS of 23.4 weeks.[23,24]

A number of ongoing trials are currently evaluating the efficacy of sunitinib in combination with standard chemotherapy regimens or other targeted therapies. In this study, we aimed to evaluate the safety and efficacy of sunitinib combined with docetaxel (tyxan) and cisplatin followed by maintenance oral vinorelbine in NSCLC patients. We lowered the dose of chemotherapeutic agents since the addition of targeted therapy would increase the efficacy of chemotherapy, while the lowered dose of chemotherapy would reduce chemotherapy-associated toxicities.

METHODS

Patients and Treatment

This open label Simon 2 stage clinical trial enrolled a total of 6 NSCLC patients who were diagnosed at Taipei Medical University Hospital between January 2009 and December 2010. These patients were all newly diagnosed and naïve for any treatments for NSCLC. Inclusion criteria were age >18 years old; presence of unresectable/metastatic NSCLC; normal liver function and renal function tests; and Eastern Cooperative Oncology Group (ECOG) < 2. Patients who had uncontrolled hypertension, clinical or radiological evidence of central nervous system metastases, serious nonhealing wound, evidence of bleeding diathesis or coagulopathy, active cardiovascular diseases or any other serious illness were excluded. Patients who used VEGF inhibitor previously, underwent any major surgery within 28 days prior to the start day of this study, underwent anticoagulants therapy or large dose aspirin (>325 mg/d) were also excluded. The study was approved by the Institutional Review Board of Taipei Medical University Hospital and informed consent was obtained from the patients.

All patients received docetaxel (40 mg) and cisplatin (50 mg) on day 1 of each cycle, with a treatment interval of 14 days. All patients received sunitinib (25 mg qd) for a total of 10 days within the 14 day intervals between treatment cycles. Patients were treated for a total of 12 cycles (24 weeks), after which patients received maintenance therapy with vinorelbine (30 mg TIW) until disease progression.

The sample size was based on a Simon's Optimal Two-Stage Design,[25] where P0 indicated probability of poor response to the drug, and P1 indicated probability of good response to the drug. For ethical considerations, this design minimizes the expected sample size when the response is P0, and allows recruitment of additional patients when the response is P1. Based on our previous preclinical study, the expected response rate was set as 35% for P0 and as 60% for P1. Using http://linus.nci.nih.gov/brb/samplesize/otsd.html, the upper limit for the first stage sample size in this study was 6 patients, and diagnosis of a poor response in the second of these 6 patients would lead to early termination of the trial. If not, the trial could progress to Stage II, where the upper limit of the number of patients was 15 (including 6 patients from Stage I). Diagnosis of poor response in the seventh patient of 15 in Stage II would lead to early termination of the study. The significance level alpha = 0.10 and power = 70%. The probability of a poor response (P0) was 0.35, and the probability of early termination at P0 was 0.65. The probability of a good response (P1) was 0.60. Based on Simon's Optimal Two-Stage Design, it is also possible to use an upper boundary for early termination if a significantly high efficacy is achieved in the first stage.[25,26]

Efficacy Analysis

The clinical responses of the patients were recorded as complete response (CR), partial response (PR), sustained disease (SD), or progressive disease (PD) according to RECIST criteria.[27] Overall response (OR) included CR and PR, and overall response rate (ORR) was calculated as the number of patients with OR among the patients evaluated. Time to ORR and time to progression-free survival (PFS) were represented as a range (min. to max.).

Safety Evaluation

All adverse events and safety parameters for all study patients were recorded during the course of the treatment period.

RESULTS

Patient Demographics

A total of 6 patients with unresectable/metastatic NSCLC were enrolled into this study. Patient demographics and clinical characteristics are described in Table 1. The study population comprised 2 males and 4 females. The age range of the patients was 42 to 56, and the number of cycles received by each patient

TABLE 1. Patients' Demographics and Clinical Characteristics (N = 6)

Patients Number	Age, y	Sex, F/M	No. of Cycles	Last examined Results During the Treatment Period								
				WBC, 103/μL	HGB, g/dL	PLT, 103/μL	NEUT, %	Glucose, mg/dL	Creatinine, mg/dL	GOT, IU/L	GPT, IU/L	LDH, IU/L	CEA, ng/mL
1	49	F	10	**9.66**	**11.8**	**6**	**0.907**	**227**	**2.4**	23	18	**653**	**84.9**
2	44	F	12	**1.58**	**5.8**	**59**	**0.475**	**113**	1.1	28	23	**323**	0.9
3	46	M	7	4.52	**11.5**	**149**	**0.609**	**96**	0.8	38	72	–	**7.9**
4	56	M	12	8.17	**8.3**	**35**	**0.826**	**140**	1.1	33	19	206	1.6
5	42	F	12	3.53	**8.7**	**206**	**0.546**	**94**	0.9	27	15	201	**7.6**
6	45	F	12	1.25	**11.2**	**68**	**0.260**	**103**	0.9	**70**	218	**302**	1.0

Normal ranges: WBC: 4.0–11.0 × 103/μL; HGB: 12–18 g/dL; PLT: 130–400 × 103/μL; NEUT: 40% to 74%; glucose: 70–110 mg/dL; creatinine: 0.5–1.3 mg/dL; GOT, GPT: 0–40 IU/L; LDH: 135–225 IU/L; CEA: <5 ng/mL.

CEA = carcinoembryonic antigen, GOT = glutamate oxaloacetate transaminase, GPT = glutamic-pyruvic transaminase, HGB = hemoglobulin, LDH = lactate dehydrogenase, NEUT = neutrophil, PLT = platelet, WBC = white blood cell.

ranged from 7 to 12. Two patients terminated earlier at cycles 7 and 10 because of disease progression in one patient and intestinal obstruction in the other patient.

Efficacy

The ORR was 66.67%. One patient had a CR, and 3 patients had a PR by the end of cycle 12 (Table 2). One patient with SD before cycle 10 and 1 patient with PD by cycle 12 died during follow-up. The OS ranged from 4 months to >60 months (the patient with SD had an OS of 6 months and the patient with PD had an OS of 4 months). The time to PFS ranged from 3 to 42 months (the patient with SD had a time to PFS of 6 months and the patient with PD had a time to PFS of 3 months).

Safety

The most common adverse events were hair loss (6/6 patients) and anemia (5/6 patients). Neurological symptoms (Grade I) were seen in 2 patients, 1 patient had Grade III fatigue, and gastrointestinal symptoms were seen in 2 patients.

DISCUSSION

In this study, a total of 6 unresectable/metastatic NSCLC patients were treated with a combination of sunitinib, docetaxel, and cisplatin followed by vinorelbine. The primary end point was response rate, using a Simon 2-stage design. The ORR was 66.7%. Four patients had an OS of >60 months. The time to PFS ranged from 3 to 42 months. The combination therapy was well tolerated.

Despite the development of a number of new chemotherapeutic regimens for NSCLC over the last few years, the improvement in OS has not been significant. Neoadjuvant chemotherapy with docetaxel–cisplatin was shown to improve OS compared with surgery alone, as well as compared with the use of adjuvant chemotherapy.[9,28] However, based on data from a number of trials that chemotherapy has reached a plateau of activity in NSCLC, there is an urgent need to integrate chemotherapy with novel targeted therapies. A number of molecules have recently been evaluated either as monotherapy or as combination therapy for NSCLC. A prospective phase II study of NSCLC patients with unresectable tumors showed that erlotinib combined with radiotherapy conferred a significantly higher response rate compared with radiotherapy alone.[29] NSCLC patients who had previously been treated with chemotherapy and who received gefitinib monotherapy showed response rates ranging from 4.5% to 18%, and 1 year survival rates of around 29%. However, in chemotherapy-naïve patients, there was no significant benefit to combining gefitinib with platinum-based chemotherapy.[30] When the study population was selected for activating EGFR mutations, targeted therapy with erlotinib or gefitinib conferred a significant advantage over platinum doublet chemotherapy.[10,31,32] Irreversible inhibitors such as afatinib which target all ErbB family RTKIs showed clinical activity in patients who acquired resistance to erlotinib and gefitinib.[33]

Sunitinib monotherapy has previously been used to treat NSCLC patients who had not responded to prior chemotherapy. Patients were either on a continuous daily dosing (CDD) schedule, or treated for 4 weeks and then rested for 2 weeks (4/2 schedule). Data from these studies showed that the CDD patients had an ORR of 2.1%, a median OS of 37.1 weeks, and a median PFS of 11.9 weeks,[34] while the 4/2 patients had an ORR of 11.1%, a median OS of 23.4 weeks, and a median PFS of 12 weeks.[24] In patients with refractory NSCLC, sunitinib used

TABLE 2. Last Follow-Up Status After Treatment for Each Patient

Patients Number	Response (CR/PR/SD/PD)	Dead or Alive	Time to PFS, mo	Adverse Events (Symptom/Grade)	Overall Survival
1	SD before Cycle 10	Dead	6	Hair loss/III anemia constipation/III nausea and vomiting/II	6 mo
2	Cycle 12 PR	Alive	22	Hair loss/III anemia	So far alive, >60 mo
3	PD	Dead	3	Hair loss/III anemia fatigue/ III	4 mo
4	Cycle 12 PR	Alive	27	Hair loss/III Anemia	So far alive, >60 mo
5	Cycle 12 PR	Alive	19	Hair loss/III anemia Neurological/I appetite changes/II nausea and vomiting/III	59 mo
6	Cycle 12 CR	Alive	42	Hair loss/III neurological/I	So far alive, >60 mo

CR = complete response, PD = progressive disease, PFS = progression-free survival, PR = partial response, SD = stable disease.

in combination with erlotinib did not significantly prolong OS or PFS compared with erlotinob monotherapy.[35,36]

A recent meta-analysis which analyzed 6 randomized controlled trials evaluated the efficacy and safety of chemotherapy combined with multi-targeted antiangiogenic TKIs compared with chemotherapy alone in patients with advanced NSCLC. While the safety profile of the 2 regimens were comparable, the combination therapy was shown to significantly increase the ORR, but not the OS.[37] Interestingly, a recent randomized phase II study showed a higher toxicity and lower OS in patients treated with either sunitinib monotherapy or patients treated with a pemetrexed–sunitinib combination compared with patients receiving pemetrexed monotherapy as second-line treatment for advanced NSCLC.[38] It is not clear if this could be due to the concentrations of the chemotherapeutic drug. These conflicting reports underline the importance of reaching a consensus on the optimal regimen for patients with advanced/metastatic NSCLC.

In this study, we used a regimen comprising the multi-target RTK inhibitor, sunitinib, in combination with docetaxel–cisplatin at a lower dosage than is generally used. This was followed by maintenance oral vinorelbine. A previous study recommended the use of a trinomial 2-stage design which treated CRs and PRs separately, since CRs more often confer a survival advantage.[39] Our data showed an ORR of 66.67%. One patient had a CR, and 3 patients had a PR by the end of cycle 12. Of the 4 surviving patients, the times to PFS were 22, 27, 19, and 42 months. Four of our 6 study patients have survived over 5 years, and this is dramatically higher compared with previous studies reporting long-term survival data. We suggest that this could be due to the lower doses of the chemotherapeutic drugs used in this study, which could increase the tolerability of the combination regimen. Since the Simon's Optimal Two-Stage design can use an upper boundary for early termination if a significantly high efficacy is achieved in the first stage,[40,41] it was possible to terminate this study early since there was a response rate of 66.7% after the first 6 patients were enrolled. Using the MedCalc software, the 95% CI for ORR = 0.667 was derived as 0.181 to 1.707. However, estimation of the 95% CI might be limited because of the small sample size. The disease status of all the 6 patients was controlled well and we were able to follow the surviving patients for at least 5 years after the treatment.

Although some phase I studies showed that sunitinib used in combination with cisplatin/gemcitabine or with docetaxel had an acceptable safety profile,[42,43] other studies showed higher toxicity in patients treated with sunitinib/pemetrexed combination compared with pemetrexed monotherapy,[38] and that sunitinib was not tolerated well in combination with standard doses of pemetrexed/cisplatin chemotherapy.[44] In our present study, the combination therapy was well-tolerated, and the most common adverse events were hair loss and anemia and neurological symptoms.

The major limitation of this study was patient recruitment. It is difficult to enroll patients in Taiwan because the National Health Insurance pays almost all the costs of targeted therapy for cancer patients. Patients therefore are not motivated to participate in clinical trials.

In conclusion, unresectable/metastatic NSCLC patients treated with a combination of sunitinib, docetaxel, and cisplatin followed by maintenance vinorelbine had an ORR of 66.7%. Four patients had an OS of >60 months, and the combination therapy was well tolerated. Larger sample sizes are warranted to validate these results.

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