ORIGINAL

Gemcitabine plus UFT combination chemotherapy as second- or third-line therapy in non-small cell lung cancer : a pilot study

Naoki Nishimura, Rika Sugiura, Hirotaka Ueda, Hiroshi Ono, Hidehito Horinouchi, Noboru Uchiyama, and Naohiko Chohnabayashi

Division of Pulmonary Medicine, St. Luke's International Hospital, Tokyo, Japan

Abstract : *Background :* Gemcitabine plus UFT combination chemotherapy are highly effective and less toxic in the first line setting in patients with non-small cell lung cancer (NSCLC). The purpose of the study is to confirm the feasibility of this regimen as second- or third-line therapy in NSCLC. *Methods :* Fifteen patients with performance status of 0-1 were enrolled. UFT (tegafur 250 mg/m^2/day) was administered orally twice a day from days 1-14, and gemcitabine of 900 mg/m^2 was administered intravenously on days 8 and 15 every three weeks on an outpatient setting. The treatment was repeated for at least 3 cycles and continued unless the disease progressed. *Results :* The response rate and the disease control rate were 6.7% and 66.7%, respectively. Grade 3-4 toxicities included neutropenia in one patient and elevation of transaminases in one patient. The mean relative dose intensity of gemcitabine and UFT were 0.93 and 0.97, respectively. *Conclusion :* High disease control rate and less toxicity suggested the potential of gemcitabine and UFT combination chemotherapy as second- or third-line therapy in NSCLC. J. Med. Invest. 55 : 260-266, August, 2008

Keywords **:** *non-small cell lung cancer, gemcitabine, UFT, uracil-tegafur, second-line chemotherapy*

INTRODUCTION

Cisplatin-based chemotherapy is beneficial as the first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) (1). Recent phase III trials showed that platinum agents in combination with the third-generation chemotherapeutic agents had the same efficacy with each other (2-4). On the other hand, the effect of second- or third-line treatment in first line-failed or relapsed NSCLC is limited. Docetaxel is the most evidence-based in the second line treatment of NSCLC (5-7). However, these studies were performed during the second-generation regimen, and docetaxel had a possibility of cross-resistance against paclitaxel, which is the most commonly used drug in the first line treatment (8). Pemetrexed and erlotinib were also good candidates for the second line chemotherapy in NSCLC (9, 10). But there is no more "evidence-based" treatment as second- or third-line therapy in NSCLC. Therefore, the establishment of another second- or third-line therapy is needed in NSCLC.

Gemcitabine is an antimetabolite and one of the standard drugs in the first line of treatment for locally advanced or metastatic NSCLC (2-4). Gemcit-

Received for publication July 3, 2008 ; accepted July 18, 2008.

Address correspondence and reprint requests to Naoki Nishimura, Division of Pulmonary Medicine, St. Luke's International Hospital, Akashi-cho 9-1, Chuo-ku, Tokyo 104-8560, Japan and Fax : +81-3-3544-0649.

abine is also expected for the second line drug. Six phase II trials showed the response rate of 7-21% and the median survival time of 22-36 weeks, and these results are almost equivalent to those of docetaxel (7).

UFT is an oral antimetabolite composed of tegafur and uracil at a fixed molar ratio of 1 : 4. Tegafur is changed to 5-FU in the body. FdUMP which is an active metabolite of 5-FU inhibits thymidylate synthase, and DNA synthesis is inhibited. Although single agent chemotherapy of UFT showed a response rate of 6.3% in advanced NSCLC (11), recent randomized phase III trials showed that postoperative adjuvant chemotherapy using 250 mg/m^2 of daily UFT improved overall survival and progression free survival significantly when compared with observation (12).

Gemcitabine is uptaken to cytosol by a transporter protein called the nucleoside transporter (13). A basic experiment showed that the expression of the nucleoside transporter was increased in the tumor cells treated with inhibitor of thymidylate synthase, such as 5-FU (14). Thus, there is a possibility that tumors treated with UFT became highly sensitive to gemcitabine because gemcitabine is over-uptaken to cytosol by over expression of the nucleoside transporter.

Gemcitabine plus UFT combination therapy is considered for their synergic effect in NSCLC. A phase I trial of gemcitabine plus UFT combination therapy in a first line setting in patients with NSCLC recommends 200 mg/m^2 of UFT b.i.d for days 1-14 with 900 mg/m^2 of gemcitabine on days 8 and 15 every three weeks (15). A phase II trial of gemcitabine plus UFT combination therapy in a first line setting showed the response rate of 41% and the median survival time of 13.2 months (16). The most common grade 3-4 toxicity was neutropenia (57%) (16). On the other hand, subjective side effects such as alopecia, neuropathy, nausea, and vomiting were few. Moreover, UFT and gemcitabine are easily administered orally, or by intravenous drip infusion in 30 minutes. Therefore, from the viewpoint of QOL, both drugs are suitable for outpatient settings as second- or third-line therapy in metastatic NSCLC that is difficult to cure. However, there are few issues described gemcitabine plus UFT combination chemotherapy as second- or third-line therapy in NSCLC. With this background, we planned a feasibility study to evaluate the feasibility of gemcitabine plus UFT combination chemotherapy as second- or third-line therapy in NSCLC.

PATIENTS AND METHODS

Eligibility

Eligible patients had histologically or cytologically proven locally advanced or metastatic NSCLC and had received one or two previous cytotoxic chemotherapy regimens and had failed or relapsed. Gefitinib was counted as one regimen when it was used as a second line regimen. Patients had histologically or cytologically defined NSCLC ; stage IV or unresectable stage IIIB ; age 20 years or over ; Eastern Cooperative Oncology Group (ECOG) performance status 0-1 ; evaluable or measurable lesion ; adequate organ function (white blood cells ≥3000/μl, absolute neutrophil count ≥1500/μl, platelets ≥100000/μl, hemoglobin ≥9.5 g/dl, serum transaminases ≤2.5 times the institutional upper limit of normal, serum total bilirubin ≤1.5 times institutional the upper limit of normal, serum creatinine ≤institutional upper limit of normal, a life expectancy of at least three months ; and written informed consent.

Patients were considered ineligible if they had interstitial pneumonia or pulmonary fibrosis on a chest X-ray, superior vena cava syndrome, uncontrollable diabetes mellitus, severe liver dysfunction with icterus, angina pectoris, acute myocardial infarction within three months, severe infection, severe psychiatric disease, pregnancy, lactating, double cancer within five years, or severe heart disease. The ethics and research committee of our hospital approved this study.

Treatment plan

All treatment was administered on an outpatient setting. Gemcitabine (900 mg/m^2) was dissolved in 200 ml of physiological saline and administered by intravenous drip infusion in 30 minutes on days 8 and 15. Dexamethasone (8 mg) was dissolved in 50 ml of physiological saline and administered by intravenous drip infusion just before the administration of gemcitabine. UFT (tegafur 250 mg/m^2/day) was administered orally twice a day in the form of a 100 mg capsule (100 mg of tegafur plus 224 mg of uracil) from days 1 to 14. The dose was rounded up or down as follows : 300 mg/body/day for a body surface area of ≤1.39 m^2, 400 mg/body/day for a body surface area of ≥1.40 m^2 and ≤1.79 m^2, 500 mg/body/day for a body surface area of ≥1.8 m^2.

On days 8 and 15, a complete blood count was performed, and the treatment was delayed one week

in case of white blood cells <2000/μl, absolute neutrophil count <1000/μl, platelets <75000/μl, and non-hematologic toxicity (except nausea, vomiting, appetite loss, fatigue and alopecia) ≥grade 3. The treatment regimen was repeated every 3 weeks and at least 3 cycles were administered unless disease progression or grade 4 non-hematologic toxicity occurred (grade 2 for interstitial pneumonia). On day 22 (day 1 of the next cycle), a complete blood count, biochemical examination, and chest X-ray were performed, and the next cycle was delayed one week in case of white blood cells <2000/μl, absolute neutrophil count <1000/μl, platelets <75000/μl, serum transaminases ≥2.5 times the institutional upper limit of normal, serum total bilirubin ≥1.5 times the institutional upper limit of normal, serum creatinine ≥institutional upper limit of normal, and non-hematologic toxicity (except nausea, vomiting, appetite loss, fatigue and alopecia) ≥grade 3. If the treatment delay was continued more than 21 days, the protocol study was cancelled.

The dose of gemcitabine was reduced by 200 mg/m^2 in case of white blood cells <2000/μl, absolute neutrophil count <1000/μl, platelets <50000/μl, and non-hematologic toxicity (except nausea, vomiting, appetite loss, fatigue and alopecia) ≥grade 3 in the prior cycle. The dose was not reduced until a cycle was completed. The dose of UFT was not changed during the study. When the dose of gemcitabine was reduced to less than 500 mg/m^2, the protocol study was cancelled.

Evaluation

The primary end points of this study were safety, feasibility, and the relative dose intensity of chemotherapeutic agents. The secondary end points were response rate and disease control rate. The relative dose intensity was calculated as follows: received dose intensity [totally administered dose of drug (mg) / total treatment duration (weeks)] / planned dose intensity [totally planned dose of drug (mg) / totally planned duration (weeks)]. The days of additional hospital visits due to any adverse event were also counted as the indicator of feasibility of the regimen. All patients received a computed tomography (CT) scan of the thorax and abdomen, magnetic resonance images (MRI) of the brain, and a radioisotopic bone scan before the treatment started. After the initial baseline imaging, an evaluation of response rates was performed after 3 cycles of treatment using the same imaging examination. The response rate was calculated according to the RECIST criteria (17). Any adverse event was graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

RESULTS

Patients' characteristics

Between October 2005 and December 2006, fifteen eligible patients with first or second line-failed or relapsed NSCLC were enrolled. The median age was 57 years (range : 39-79 years). ECOG Performance status was 0 in 7 patients and 1 in 8 patients. Twelve patients had stage IV disease and three patients had stage IIIB disease. Thirteen patients had adenocarcinoma and two patients had undifferentiated NSCLC. The first line therapy was carboplatin plus paclitaxel therapy for 13 patients, cisplatin plus vinorelbine for one patient, and single agent docetaxel therapy for one patient. The previous therapy just before gemcitabine plus UFT therapy was gefitinib for 8 patients, carboplatin plus paclitaxel for 5 patients and docetaxel for 2 patients. Five patients had previously received palliative radiotherapy and 3 patients had received gamma knives for brain metastasis. There was no patient who had received both Linac and gamma knife therapies. These characteristics are shown in Table 1.

Table 1 Patient characteristics

Gender	
Male / Female	9 / 6
Age	
Median (range)	57 (39-79)
Performance status (ECOG*)	
0/1	7 / 8
Stage	
IIIB / IV	3 / 12
Histology	
Adenocarcinoma / others	13 / 2
First line therapy	
Carboplatin plus paclitaxel / other chemotherapy	13 / 2
Previous therapy just before gemcitabine plus UFT therapy	
Gefitinib / carboplatin plus paclitaxel / docetaxel	8 / 5 / 2
Previous palliative radiotherapy	
None / Linac / gamma knives for brain metastasis	7 / 5 / 3

* : Eastern Cooperative Oncology Group

Response

Fourteen patients among 15 eligible patients were evaluable for response. For one patient it was impossible to evaluate response because the treatment had to be cancelled after one cycle due to toxicity. One patient's disease became remarkably progressive after 2 cycles of treatment, and the treatment was cancelled because of the patient's preference. One patient achieved a partial response (1/15, 6.7%) (Table 2). Nine patients showed stable disease (9/15, 60.0%), and four patients showed progressive disease (4/15, 26.7%) (Table 2). Disease control rate was 66.7% (10/15).

Table 2 Treatment characteristics

Total number of cycles	59
Median number of cycles (range)	3 (1-7)
Number of administered courses	
1	1
2	1
3	7
4	0
5	2
6	3
7	1
Median interval days between cycles (range)	21 (21-28)
Number of unexpected visit to the hospital due to adverse event	3 (in 59 cycles)
Relative dose intensity of gemcitabine	
Mean±SD*	0.93 ± 0.10
Median (range)	1 (0.75-1)
Relative dose intensity of UFT	
Mean±SD	0.97 ± 0.07
Median (range)	1 (0.75-1)
Response	
CR	0
PR	1
SD	9
PD	4

* : standard deviation

Feasibility and toxicity

All patients were evaluable for toxicity and feasibility. A total of 59 cycles was administered in 15 patients. The median number of cycles was 3 (range : 1-7). The median interval between cycles was 21 days (range : 21-28). The number of unexpected visits to the hospital due to adverse events was only 3 in total 59 cycles. The mean and the median relative dose intensity of gemcitabine were 0.93 and 1 (range : 0.75-1), respectively. The mean and the median relative dose intensity of UFT were 0.97 and 1 (range : 0.75-1), respectively. These profiles of feasibility are shown in Table 2.

The main toxicity was hematologic toxicity. Grade 2 neutropenia occurred in 8 patients. However, Grade 3 neutropenia was shown only in one patient and treatment was delayed. Anemia occurred with Grade 1 in 7 patients and Grade 2 in 4 patients. Thrombocytopenia was relatively mild with Grade 1 in 8 patients and Grade 2 in 1 patient. One patient showed Grade 3 elevation of transaminases after the first cycle of treatment and the second cycle of treatment was cancelled because of the patient's preference. In the subjective side effects, fatigue was one of the major symptoms in this treatment with Grade 1 in 4 patients and Grade 2 in 4 patients. Appetite loss was shown in 6 patients with Grade 1, and 2 patients in Grade 2. However, nausea and vomiting was minimal. Grade 1 alopecia occurred in 5 patients, but they received chemotherapy containing paclitaxel or docetaxel just before gemcitabine plus UFT treatment. There was no Grade 4 toxicity. No patient needed hospitalization during treatment. No patient died due to toxicity. The profiles of toxicity are shown in Table 3.

Table 3 Hematologic and non-hematologic toxicities (n=15)

	Grade*			
Toxicity	1	2	3	4
Hematologic toxicity				
Leucopenia	7†	5	-	-
Neutropenia	-	8	1	-
Anemia	7	4	-	-
Thrombocytopenia	8	1	-	-
Non-hematologic toxicity				
Transaminases	-	-	1	-
Alopecia	5	-	-	-
Appetite loss	6	2	-	-
Diarrhea	2	1	-	-
Fever up	1	-	-	-
Fatigue	4	4	-	-
Nausea	2	1	-	-
Skin eruption	-	1	-	-
Stomatitis	1	-	-	-
Vomiting	1	-	-	-

* : National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
† : Data were shown in the number of patients.

DISCUSSION

In this pilot study, we showed the feasibility and

toxicity of gemcitabine plus UFT combination chemotherapy. Gemcitabine plus UFT combination chemotherapy was well-tolerated in second- or third-line setting in NSCLC. Because there were very few Grade 3-4 adverse events, the number of unexpected visits to the hospital due to adverse events was quite few during the treatment (Table 2, 3). Therefore, treatment delay was almost free and the relative dose intensities of both gemcitabine and UFT were very high (Table 2). These results of feasibility were especially good compared with other second line regimens (5-7, 9, 10). Moreover, 10 out of 15 (66.7%) patients' disease were controlled (CR+PR+SD) after 3 cycles of treatment, and we could repeat the treatment for 5 cycles in 2 patients, 6 cycles in 3 patients, and 7 cycles in one patient (Table 2). Less toxicity also helped the repeat of cycles. We also found that the toxicity was not accumulated after the repeat of cycles. There were a few subjective side effects such as alopecia and emesis (Table 3), and gemcitabine and UFT are easily administered by a 30-minute intravenous drip infusion or orally. Therefore, from a QOL viewpoint, gemcitabine plus UFT combination chemotherapy were considered suitable for an outpatient setting. High disease control rate and less toxicity suggested the potential of gemcitabine and UFT combination chemotherapy for an outpatient setting as second- or third-line therapy in metastatic NSCLC that is difficult to cure.

Although 400 mg/m^2 of UFT was administered in a phase II trial of first line-gemcitabine plus UFT combination chemotherapy (16), we administered 250 mg/m^2 of UFT because recent randomized phase III trials showed that postoperative adjuvant chemotherapy using 250 mg/m^2 of daily UFT improved overall survival and progression free survival significantly compared with observation (12). We assumed that 250 mg/m^2 of UFT was enough for efficacy. We thought the meaning of UFT in the gemcitabine plus UFT combination therapy was not the cytotoxic agent but the sensitizer of gemcitabine through the effect of overexpression of the nucleoside transporter (13, 14). We considered that 250 mg/m^2 of UFT might be enough for the sensitizer.

One patient showed Grade 3 elevation of transaminases and the treatment was cancelled because of the patient's preference. This patient had experienced Grade 3 elevation of transaminases in the previous treatment (gefitinib), but had no hepatitis virus. Gemcitabine, especially in combination therapy, is known to have liver toxicity. A previous report of a phase II trial of gemcitabine plus vinorelbine therapy showed 22.5% of Grade 3-4 elevation of transaminase (18). It is said that liver dysfunction caused by gemcitabine is transient and reversible (18). But we have to remark that liver toxicity can also be found in the gemcitabine plus UFT therapy

A recent phase II trial reported by Chen, *et al.* showed the effectiveness of gemcitabine plus uracil-tegafur combination chemotherapy in NSCLC patients failing previous chemotherapy (19). In the study, the response rate achieved 15.6%, and Grade 3-4 hematologic toxicities were observed in 6.7-17.8% of patients (19). On the other hand, non-hematologic toxicities were minimal and mild (19). The profile of efficacy and toxicity in our study was similar to Chen's result. The treatment schedule was different between our study and Chen's study (19). We administered UFT on days 1-14 and gemcitabine on days 8 and 15 every three weeks. On the other hand, Chen, *et al.* administered UFT on days 1-14 and gemcitabine on days 1 and 8 every three weeks (19). We considered that the pretreatment of tumor cells with UFT caused the increase of sensitivity against gemcitabine through the overexpression of nucleoside transporter in tumor cells (13, 14). Therefore, we recommend administering gemcitabine on days 8 and 15 after the initial administration of UFT.

The limitation of the study was the sample size in the feasibility study. Thus, a phase II trial of gemcitabine plus UFT combination chemotherapy using our schedule would be required to confirm the efficacy. In conclusion, gemcitabine plus UFT combination chemotherapy as second- or third-line therapy in NSCLC was well-tolerated with less toxicity. This regimen would be one of the hopeful treatments in second or third line settings for patients with locally advanced or metastatic NSCLC.

ACKNOWLEDGEMENTS

We thank Mr. Kazuhiro Kiyosawa for his help in preparing the protocol.

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