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Comparison between Prolonged Administration of Oral Etoposide and UFT Combined with Intravenous Cisplatin-based Chemotherapy in Postoperative Non-small Cell Lung Cancer: a Randomized Trial

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Oral administration of etoposide or UFT is generally used in outpatient treatment of non-small cell lung cancer (NSCLC) after surgery in Japan. We examined the effectiveness of etoposide and UFT with relation to disease-free survival, overall survival and toxicity in postoperative NSCLC patients. In this study, a total of 50 patients were randomized to receive either, 25mg/day of etoposide, on a 2 week cycle (Group I-25 cases) or 300mg/day of UFT, continuous administration (Group II-25 cases), after a Mitomycin C, Cisplatin and Vindesine, intravenous (i.v.). Disease-free and overall survival were better in Group II with 20 complete cases than in Group I with 15 complete cases. Furthermore, Group II achieved better disease-free and overall survival rates than Group I with reference to stage IIIA and lymph node metastasis groups. There were no instances of severe toxicity in either group. Results of this study showed that prolonged oral administration of 25mg/day of etoposide is ineffective compared with oral UFT in NSCLC patients after surgical treatment. New randomized clinical trials of 50mg/day of etoposide will be necessary to determine usefulness and toxicity.

Key words: etoposide, UFT, postoperative chemotherapy

Introduction

Chemotherapy has proven to be ineffective in treating non-small cell lung cancer (NSCLC), while the number of NSCLC patients are increasing in Japan and Asia. Many institutes are carrying out clinical trials using new agents for advanced NSCLC. Chang et al.[1] and Murphy et al.[2] have reported that these agents have produced higher response rates in advanced NSCLC. However, tests of new agents are still being conducted to determine if toxicity will be a problem.[3] At present, Cisplatin (CDDP)-based chemotherapy is still one of the most commonly used postoperative chemotherapies for recurrence prevention in NSCLC patients after surgical treatment.

Oral administration of anticancer drugs, if there is no severe toxicity problem, needs to be introduced in outpatient treatments to contribute to the increase of the QOL of the patient after surgical resection. Presently, two drugs, etoposide and UFT are used as oral administration in postoperative chemotherapy. Although clinical trials of UFT alone were performed in several institutes[4~6], etoposide has been used in few trials following scientific protocols. To the authors' knowledge there are no reports regarding comparisons between prolonged oral administration of UFT and etoposide after surgery, although there is a report of etoposide + UFT combined with Carboplatin in advanced NSCLC.[7]

The purpose of this clinical trial have shown whether or not oral administration of either etoposide or UFT has an impact on prognosis in NSCLC patient populations after surgery.

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Patients and Methods

The medical records of 50 patients who underwent thoracotomy for the treatment of NSCLC at the four collaborative institutes in Kyushu area between May,

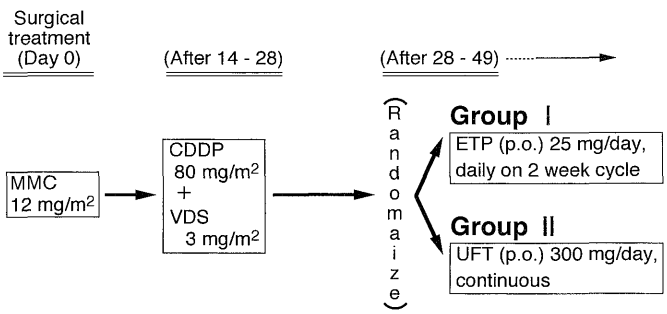
1991 and December, 1993 were reviewed to identify patients who had undergone a curative or a relative curative operation (p-stage I, II and IIIA) according to pathological findings. Patients were assigned a pathological stage in accordance with the staging system of The General Rule of The Japan Lung Cancer Society (The 3rd Edition)[8].

Eligibility criteria included : 1) Patients less than 75 years old. 2) Patients with no prior therapy and a Performance status of 0, 1 or 2. 3) Hematological examinations with WBC$<$4000/mm^3, PTL$<$10000/mm^3, Cr$>$1.5mg, CCr$<$60ml/min and up to 2 times normal GOT and GPT. Patients with recent cardiac disease, infection and double cancers were excluded. All patients and/or families gave informed consent. The study was a randomized trial by closed envelope method.

Treatment methods were administered as follows: Immediately, 12mg/m^2 of Mitomycin C were administered intravenously after completion of surgical resection. Next, 80mg/m^2 of CDDP and 3mg/m^2 of Vindesine were administered intravenously once from 2 to 4 weeks later. After a hematological examination, the patients were divided into two groups (Group I and II) by closed envelope method. From 2 to 3 weeks after administration of CDDP and Vindesine, Group I received an oral dose of 25mg/day of etoposide and etoposide was given daily on 2 week cycles. Group II received daily 300mg oral doses of UFT. During treatment, hematological checks and X-rays or CT examinations were performed at 2 to 4 week intervals (Fig. 1). Oral etoposide and UFT were discontinued if the leukocyte count fell below 3000/mm^3, the platelet count fell below 7000/mm^3 or the liver or kidney showed signs of damage. It was also discontinued when a chief doctor diagnosed serious complications or patients disapproved of the trial.

The condition of Patients were evaluated regarding disease-free survival, overall survival and toxicity. Toxicity criteria were evaluated by the Japan Society of Clinical Oncology of Vol. 21 in 1986. Patients who received oral doses of etoposide or UFT for more than 6 months were considered "complete cases", while those receiving treatment for less than 6 months were considered "incomplete cases". G-CSF did not be used in complete and incomplete cases of this study.

Differences between patient characteristics in the 2 groups were evaluated using the χ^2 test. Disease-free and overall survival were calculated from the randomized data by the Kaplan-Meier method and the differences between the 2 groups were analyzed by a log-rank test and generalized wilcoxon test. A p value of less than 0.05 denoted the presence of statistically significant differences.



MMC= mitomycin C, CDDP= cisplatin, VDS= vindesine, ETP= etoposide

Fig. 1 Regimen of treatment methods in Group I (etoposide) and Group II (UFT).

Results

A total of 50 patients entered into this study. 15 out of 25 in Group I were complete cases, nine were incomplete cases consisting of 5 recurrences, 1 postoperative pneumonia, 1 disapproval and 2 myelosuppression, and an ineligible case was administrated other anticancer drug. 20 out of 25 in Group II were complete cases, 3 were incomplete cases with recurrence, and 2 were ineligible cases who were administrated other anticancer drug.

There were no differences in clinicopathological features of patient characteristics between Group I and II in complete cases (Table 1). In complete cases, the actual 1-year disease-free survival rates of Group I and II were 85.7% and 100%, respectively, while 3-year disease-free survival rates for Group 1 and 2 were 63.5% and 87.5%, respectively. Disease-free survival rates were better in the Group II than in the Group I, though rates between the two groups were not statistically significant (Fig. 2A). 1- and 3-year overall survival rates in Group I were 93.3% and 65.0%, respectively, while Group II rates were 100% and 94.1%, respectively. Again, there was no statistically significant difference in overall survival rates between the two groups (Fig. 2B). Additionally, data were analyzed according to the classification of p-stage. In stage IIIA, disease-free and overall survival rates were better in the Group II than in the Group I, with a statistically significant difference between the two groups (Fig. 3). The relationship between survival and the condition of lymph nodes was also analyzed between two groups. There were no statistical significance for disease-free and overall survival rates in non-lymph node metastasis group, while in lymph node metastasis groups, disease-free and overall survival rates were significantly better in the Group II

Table 1. Characteristics in complete cases of Group I (etoposide) and Group II (UFT)

Variables	Group I (n=15)	Group II (n=20)	P-value
Sex			
male	9	15	NS*
female	6	5	
Age (year)			
<65	9	14	NS
≧65	6	6	
Pathological stage			
I	8	10	
II	2	3	NS
III A	5	7	
Performance status			
0	16	17	
1	0	1	NS
2	0	0	
Histological type			
squamous	2	7	
adeno.	13	10	NS
large	0	3	
The term of drug administration (day)	296~719	227~998	NS
median	(353)	(359.5)	

* NS : Non stastically significance

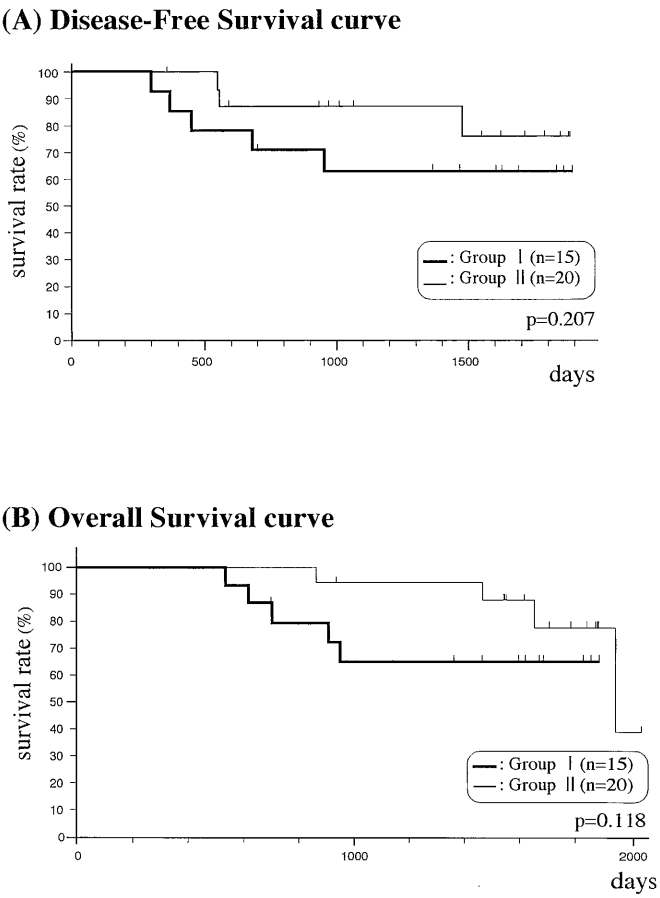


Fig. 2 Disease-free and overall survival curves for complete cases in Group I (etoposide) and Group II (UFT).

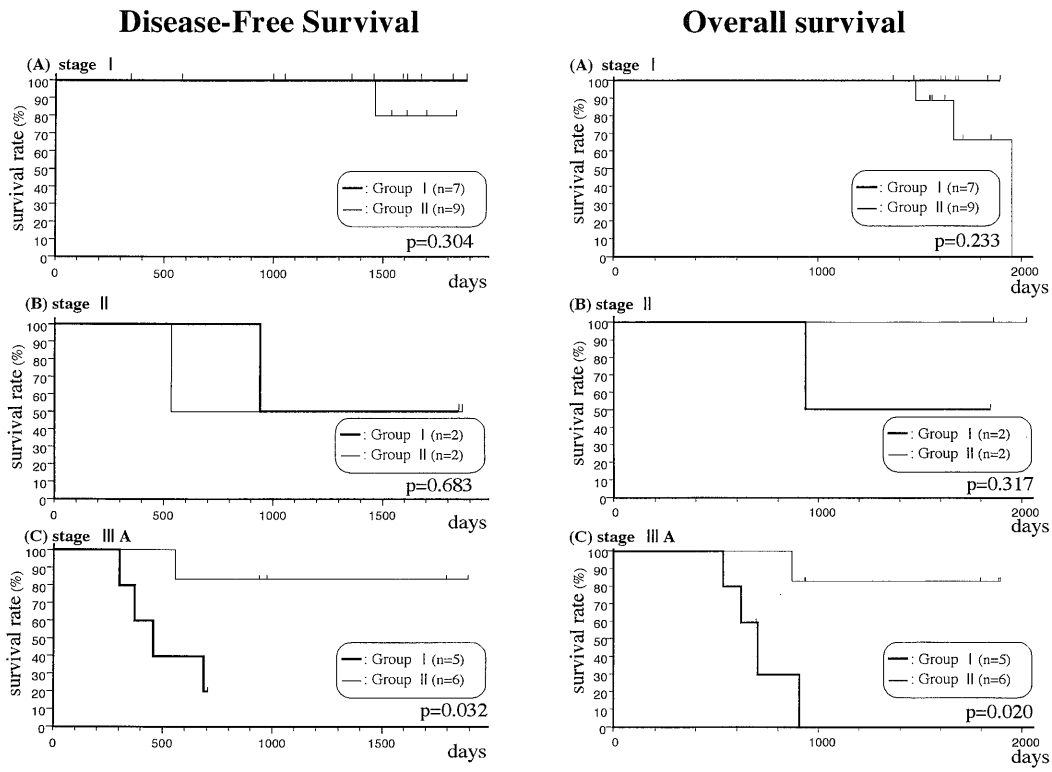


Fig. 3 Disease-free and overall survival curves for complete cases in each stage (stage I: (A), stage II: (B), stage IIIA: (C)).

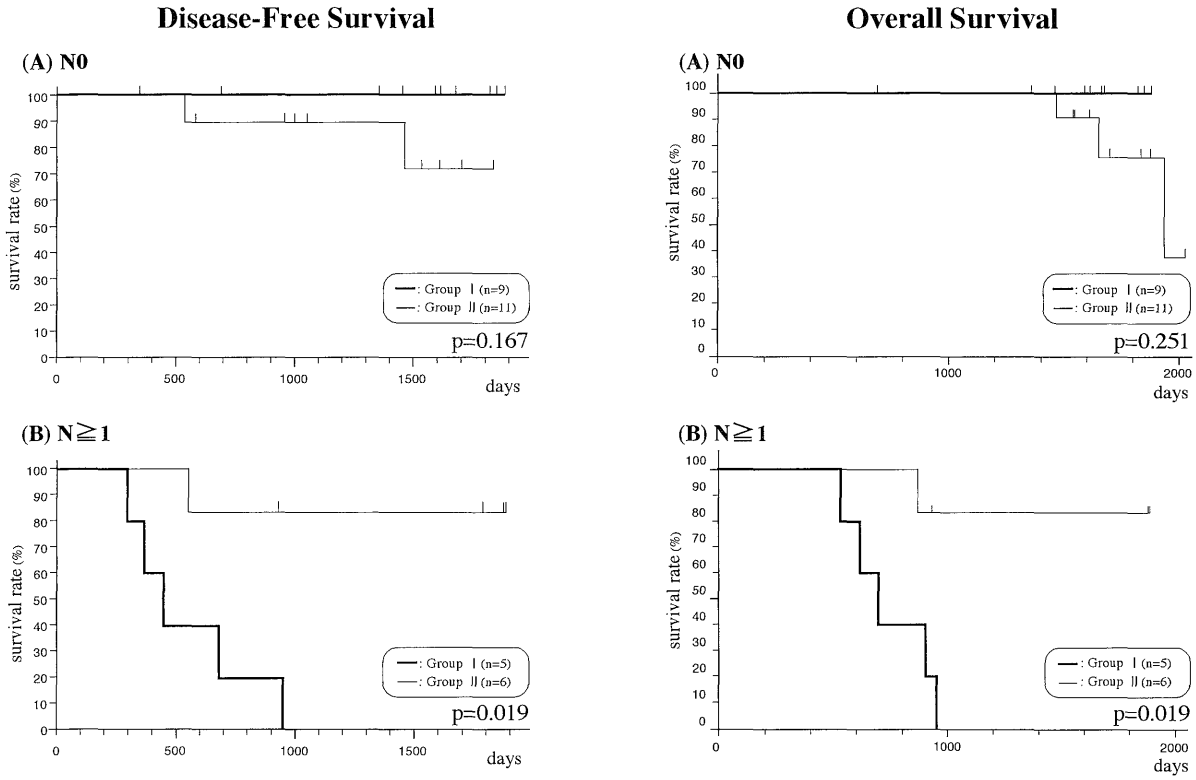


Fig. 4 Disease-free and overall survival curves for complete cases with non-lymph node metastasis group (A) and lymph node metastasis group (B).

than in the Group I (Fig. 4). There were no statistical significance for T-factor, histological type and grading between the two groups. Toxicity in 47 patients of incomplete and complete cases is given in Table 2. One incomplete patient in Group I stopped administration of etoposide because of a Grade 3 gastrointestinal symptom after 4 months. And, there were mild toxicities of Grade 1 and 2 in the great majority of patients in Groups I and II.

Discussion

Prolonged administration of oral etoposide combined with CDDP is sometimes used to treat advanced NSCLC patients. Willer et al.[9] reported that a 37% response rate was obtained with oral etoposide for the cycle of 21 day administration after a CDDP i.v. in advanced NSCLC. Recently, Jeremic et al.[10] showed that prolonged administration of oral etoposide combined with a Carboplatin i.v. produced a significantly better prognosis than that of Carboplatin alone in advanced NSCLC. Additionally, one paper reported that oral administration of etoposide decreased tumor size in a recurrent patient after surgical treatment.[11] Conversely, Hayasaka et al.[12] has pointed out that adjuvant postoperative chemotherapy with oral etoposide was not effective treatment for improvement

Table 2. Toxicity in all patients (n=47) in Group I (etoposide) and Group II (UFT)

Data abnormality and Symptom	Group I (n=24)						Group II (n=23)					
	Grade					Total	Grade					Total
	0	1	2	3	4	Toxicity	0	1	2	3	4	Toxicity
Haematologic												
Leucocyte	11	3	8	2		54.2%	14	6	2	1		39.1%
Haemoglobine	18	3	3			25.0%	20	3				13.0%
Platelet	23	1				4.2%	22		1			4.3%
Hepatic												
GOT,GPT	23		1			4.2%	22	1				4.3%
Renal												
Creatinine	24					0.0%	22	1				4.3%
Creatinine Crearance	23		1			4.2%	23					0.0%
Al-p	24					0.0%	22		1			4.3%
hematuria	23	1				4.2%	23					0.0%
proteinurea	22		2			8.3%	23					0.0%
Gastrointestinal												
anorexia	8	4	11	1		66.7%	7	4	10	2		69.6%
nausea/vomiting	8	4	11	1		66.7%	5	2	13	3		78.3%
diarrhea	23		1			4.2%	22	1				4.3%
Others												
peripheral neuropathy	23	1				4.2%	23					0.0%
fever	23	1				4.2%	23					0.0%
alopecia	23	1				4.2%	21	2				8.7%
malaise	21	3				12.5%	20	3				13.0%

Toxicity grades were evaluated by the Japan Society of Clinical Oncology of Vol. 21 in 1986.

of disease-free and overall survival, though toxicity was not severe and long term oral administration was possible.

Concerning oral administration of UFT after surgical treatment, Tomita et al.[13] reported that groups treated with UFT alone or UFT combined with a Cisplatin and Vindesine i.v. obtained lower recurrence rates than a group which surgery was the only treatment. Particularly, they recognized the usefulness of UFT alone after surgery. The UFT only group produced the best results among the three in their study. In this study, the authors compared etoposide and UFT, and whether prolonged oral administration was useful in outpatients after surgical treatment. Results showed that oral administration of UFT gave a better prognosis than that of etoposide in complete patients group, though there was no statistical significance for disease-free and overall survival rates between the two groups. Furthermore, the authors examined the relationship among prognostic factors in detail. For stage IIIA patients, the anticancer effect of UFT was superior to etoposide. This study showed the same result as the reports of Tomita et al.[13] and Okimoto et al.[14]. Additionally, for lymph node condition of a strong prognostic factor, UFT showed better effectiveness than etoposide for the lymph node metastasis groups.

However, there were several problems in this study. The first problem was dose concentration. It was pointed out that an oral dose of 25mg/day of etoposide was not effective for NSCLC patients, because it does not provide a high enough concentration in the blood for treatment of lung cancer. Therefore, a etoposide dose of 50mg/day is needed to obtain any anticancer effect[15,16]. However, in earlier clinical experiments, the authors couldn't use the dose of 50mg/day because of the side effects of myelosuppression and gastrointestinal damages same as Uchida et al.[17]. The second problem is the difference in administration methods. Difference between continuous (UFT) and 2 week cycle (etoposide) administration is a problem. The third problem was too many incomplete patients in the etoposide group, 5 patients had local and distant metastasis in early phase after surgical resection.

In a realistic situation, authors compared oral etoposide and UFT in the dose limitations of general clinical treatment. The results of this study suggest that adjuvant chemotherapy of oral etoposide should not be use in NSCLC patients after surgical treatment although new clinical trials of 50mg/day will be necessarily. The authors believe that oral UFT may be a safe and effective anticancer drug for outpatients after surgical treatment of NSCLC.

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