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EFFICACY OF A NEW 5-FLUOROURACIL DERIVATIVE, BOF-A2, IN ADVANCED NON-SMALL CELL LUNG CANCER

A multi-center phase II study

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Oral BOF-A2 (Emitefur), a new derivative of 5-fluorouracil (5-FU) containing both 1-ethoxymethyl-5-FU (EMFU), a masked form of 5-FU, and 3-cyano-2,6-dihydroxypyridine (CNDP), an inhibitor of 5-FU degradation, was administered to 71 non-small cell lung cancer (NSCLC) patients in a multi-center phase II study. The patients were scheduled to receive at least 2 courses of treatment, each consisting of 200 mg twice daily for 2 weeks followed by a 2-week rest period. Out of 62 evaluable patients, 11 (18%) responded (8 of 44 adeno- and 3 of 15 squamous cell carcinomas). Thirty-four patients showed no change and 17 progressive disease. The incidences of grade $\geqslant 2$ hematologic toxicity were 5–8% for leukopenia, thrombocytopenia, and anemia. The incidences of non-hematologic toxicity of grade $\geqslant 2$, such as anorexia, nausea/vomiting, and diarrhea, were close to 20% or lower.

BOF-A2 (3-[3-(6-benzoyloxy-3-cyano-2-pyridyloxycarbonyl)benzoyl]-1-ethoxymethyl-5-fluorouracil) is a new 5-FU derivative developed in 1989 by Fujii et al. (1) for oral use in cancer chemotherapy. It contains 1-ethoxymethyl-5-fluorouracil (EMFU), a masked form of 5-FU, and 3-cyano-2,6-dihydroxypyridine (CNDP), an inhibitor of 5-FU degradation by dihydrouracil dehydrogenase (2). BOF-A2 is degraded to EMFU and CNDP in vivo, with the EMFU gradually being converted into 5-FU by liver microsomes whereas the CNDP inhibits degradation of 5-FU, resulting in a long lasting concentration of 5-FU in the blood (3) (figure). Animal experiments have suggested that this drug has potent antitumor activity in experimental tumor models and against human cancers xenografted to nude mice, including cell lines with a low sensitivity to 5-FU and its derivatives. The reason for this is assumed to be long persistence of a high 5-FU level in the tumor tissue (4, 5).

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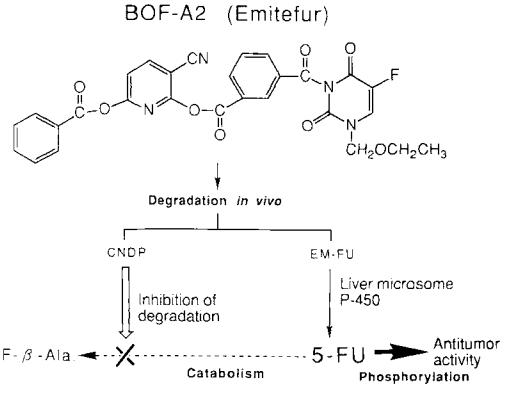

Figure. Action mechanism of BOF-A2 (Emitefur).

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A phase I study estimated the maximum tolerated dose at 400 mg/m^2 p.o. daily for 4 weeks and showed that the dose-limiting toxicities were anorexia, diarrhea, leukopenia, and thrombocytopenia (6). In a succeeding early phase II study, therapeutic response were observed in patients with gastric, colorectal, pancreatic and breast cancer, and NSCLC (7). Based on those results, a multicenter phase II study of BOF-A2 was carried out in patients with NSCLC by the BOF-A2 Study Group in Japan.

Material and Methods

Patients. Enrollment criteria for the study were: histological proof of NSCLC, measurable or evaluable lesion, performance status of 0 to 3 (ECOG), no chemotherapy within 4 weeks, or radiotherapy within 6 weeks before entry, minimum life expectancy of 2 months, age 16–75 years, WBC $> 3 \cdot 10^9$/l, platelets $> 100 \cdot 10^9$/l, GOT and GPT < 100 IU or below twice the normal limits, and serum creatinine < 20 mg/l. Informed consent was obtained from each patient before entry.

Treatment schedule. BOF-A2 in powder form at a concentration of 50% was orally administered at a dose of 200 mg twice daily after breakfast and supper for 2 weeks followed by a 2-week rest period. The protocol called for at least two courses of the treatment.

Evaluation. Tumor response was evaluated by extramural reviewers according to the criteria of the Japan Lung Cancer Society. Complete response (CR) was defined as complete resolution of all measurable or evaluable lesions and no new lesion detectable for a period of at least 4 weeks. Partial response (PR) was defined as $\geqslant 50\%$ decrease in the sum of the products of the perpendicular diameters of measurable lesions without appearance of new lesions or progression of assessable lesions for at least 4 weeks. No change (NC) was defined as $< 50\%$ decrease or $< 25\%$ increase in the sum of the perpendicular diameters of measurable lesions without progression of tumor-related secondary lesions or appearance of new lesions for at least 4 weeks. Progressive disease (PD) was defined as $\geqslant 25\%$ increase in the sum of the perpendicular diameters of any measurable lesion or progression or appearance of any evaluable lesion. Toxicities were assessed according to the grading criteria of the Japan Society for Cancer Therapy (8), which were modified from WHO criteria (9). The actually delivered dose rate of BOF-A2 was calculated as follows: [actually delivered dose (mg/body/day $\times$ total days of administration) during the first 8-week period/projected dose (400 mg/body $\times$ 14 days $\times$ 2 courses]. The duration of response was measured from the start of treatment until progression of the disease. The survival time was calculated as the time from the start of treatment until death or final follow-up.

Results

From May 1990 to July 1992, 71 patients were entered into the study by 18 institutions. The male-to-female ratio was 55:16 with an overall median age of 66 years. Most patients had performance status 1 or 2 and were clinical stage IIIB or IV. There were 49 adenocarcinomas, 17 squamous cell carcinomas and 5 large cell carcinomas. Thirty-eight patients had had prior chemotherapy, including 5-FU treatment in 6 cases (Table 1). Out of the 71 patients enrolled, one case who had had prior radiotherapy within the preceding 6 weeks was found to be ineligible. Eight patients were judged to be unevaluable for response, of whom 2 died of non-malignant diseases before completion of the first or second course of treatment, one case died of disease progression on day 6, which was judged to be too early for response evaluation. Two cases with gastrointestinal symptoms of grade 2 or stomatitis of grade 1 refused to receive further treatment at day 8 and 11, one previously untreated patient exhibited bone marrow suppression of grade 4 at day 12, and 2 patients had inadequate documentation. Thus, 62 cases were evaluable for response whereas 65 were available for toxicity assessment. A total of 207 courses of oral BOF-A2 were delivered, with a median of two courses (range: 0.5 to 15) to each patient. Eight patients received 5 or more courses of the treatment.

Response. Response rates of BOF-A2 according to patient characteristics are shown in Table 2. There were 11 partial responses out of 62 evaluable cases, with an overall response rate of 17.7% (95% confidence interval 8.2 and

Table 1

Patient characteristics

Number of patients enrolled	71
Number of patients evaluable for response	62
Male/female	55/16
Median age (years)	66 (29–76)
Performance status (ECOG)	
0	5
1	47
2	12
3	7
Clinical stage	
I	2
II	1
IIIA	11
IIIB	14
IV	43
Cell type	
Adenocarcinoma	49
Squamous cell carcinoma	17
Large cell carcinoma	5
Prior chemotherapy	
Yes	38
(5-FU)	(6)
No	33

Table 2

Response rates of BOF-A2 according to patient characteristics (n = 62)

Overall	11/62 (17.7%)*
Sex	
Male	8/49 (16.3%)
Female	3/13 (23.1%)
Prior chemo- or radiotherapy	
Yes	4**/36 (11.1%)
(5-FU)	(0/6)
No	7/26 (26.9%)
Cell type	
Adenocarcinoma	8/44 (18.0%)
Squamous cell carcinoma	3/15 (20.0%)
Large cell carcinoma	0/3 (0%)
Clinical stage	
I–II	0/2 (0%)
IIIA	0/9 (0%)
IIIB	3/12 (25.0%)
IV	8/39 (20.5%)
Performance status	
0–1	9/48 (18.8%)
2–3	2/14 (14.3%)

* 95% confidence interval = 8.2 ~ 27.3%
** All 4 responders had previously recieved platinum derivatives in combination with other antincancer agents.

27.3%). Thirty-four patients were judged as NC. Seventeen patients showed disease progression. Median duration of response in the cases with partial response was 84 days. Overall median survival time was 283 days. No significant difference in the response rate was seen between males and females, ECOG performance status 0–1 and 2–3, clinical stage IIIB and IV, or by cell type. A higher response rate, 26.9%, was obtained for the cases with no prior chemo- or radiotherapy, as compared with 11.1% for the cases with prior treatment, but this difference was not statistically significant. All 4 responders with prior chemotherapy had been treated with platinum derivatives in combination with other anticancer agents, whereas none of the patients with 5-FU pretreatment responded to BOF-A2. The actually delivered dose rates during the first 8 weeks were on average 94% for responders and 92% for non-responders.

Toxicity. Incidences of hematologic toxicity of grade 2 or higher were 7.7% for leukopenia, 7.7% for thrombocytopenia, and 4.6% for anemia (Table 3). It was noteworthy that grade 3 or higher hematologic toxicities were seen in less than 5% of the cases. Concerning non-hematologic adverse effects of grade 2 or higher, anorexia was noted in 18.5%, nausea and vomiting in 10.8%, diarrhea in 9.2%, stomatitis in 10.8% and dermatologic toxicity in 1.5%. In some cases, gastrointestinal symptoms were considered to be the dose-limiting factors.

Table 3

Incidence of hematologic and non-hematologic toxicity of BOF-A2 (n = 65)

Toxicity	⩾ grade 2	⩾ grade 3
Leukopenia	5 (7.7%)	3 (4.6%)
Thrombocytopenia	5 (7.7%)	2 (3.1%)
Anemia	4 (6.2%)	3 (4.6%)
Anorexia	12 (18.5%)	4 (6.2%)
Nausea/vomiting	7 (10.8%)	3 (4.6%)
Diarrhea	6 (9.2%)	3 (4.6%)
Stomatitis	7 (10.8%)	3 (4.6%)
Pigmentation	4 (6.1%)	1 (1.5%)

Toxicity was graded according to the criteria of the Japan Society for Cancer Therapy (8) which were modified from WHO criteria.

Discussion

5-fluorouracil has been extensively used in the treatment of certain types of cancer, including non-small cell lung cancer in combination with other anticancer drugs (10, 11). However, 5-FU is rapidly degraded by dihydrouracil dehydrogenase, mainly in the liver, and is excreted in the urine as 2-fluoro-β-alanine. Therefore, various 5-FU derivatives, such as tegafur (12, 13), UFT (14), and 5'-deoxy-5-fluorouridine (5'DFUR) (15, 16), have been developed to potentiate the anticancer activity by preventing 5-FU degradation or by obtaining a sustained concentration of 5-FU in the blood. However, none of these analogs has been successful in achieving an antitumor activity of ⩾15%, which has been adopted as the minimum response rate required of an active drug in single-agent phase II studies in non-small cell lung cancer patients (17).

BOF-A2 was synthesized under a concept similar to the above analogs. In the early phase II study, we obtained promising results with a response rate of 17% (2/12) in non-small cell lung cancer (6). Matsui et al. (18) reported good transfer of 5-FU to the cancer tissue and prolonged high 5-FU concentrations in the cancer tissue after oral administration of BOF-A2 to lung cancer patients, as compared with oral administration of UFT, indicating a potent anticancer effect of this drug. In the present study, we observed 11 partial responders out of 62 evaluable cases, with an overall response rate of 17.7%. Of a number of agents evaluated in phase II studies for the treatment of NSCLC, less than 10 drugs have produced response rates ⩾15% in previously untreated patients (17, 19). The present study demonstrates that orally administered BOF-A2 produces a response rate comparable to that obtained with intravenously administered agents. The patients who had had prior therapy seemed to be less responsive than chemotherapy-naïve patients, whereas it was noteworthy that all of 4 responders with prior therapy had been treated with combination chemotherapy including cisplatin or carboplatin. It is also of interest to note that BOF-A2 was active against both adenocarcinomas and squamous

cell carcinomas, with response rates of 18% and 20% respectively.

As for hematologic toxicity, grade 3 or higher leukopenia was seen in only 4.6%, and thrombocytopenia and anemia were each seen in 3.1%. The incidences of major non-hematologic toxicity of grade $\geqslant 2$ were near 20% or lower, including grade 3 toxicities in only 1 to 4 patients. Thus, the toxicity profile of this drug was usually mild and tolerable. Dose-limiting toxicities were considered to be gastrointestinal symptoms, which disturbed continuous oral administration of the drug in some patients. However, most patients tolerated at least two courses of the treatment, with a maximum of 15 courses in a case. Through the oral use of this active and less toxic agent, the maintenance of the quality of life would be anticipated when combined with more toxic agents in practical use.

In conclusion, the present study indicates that BOF-A2 is active in the treatment of NSCLC, with a significant response rate and tolerable toxicity.

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