A phase II trial of Ifosfamide combination with recommended supportive therapy for recurrent SCLC in second-line and heavily treated setting

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Abstract

Purpose The response rate of ifosfamide (IFM) monotherapy for small-cell lung cancer (SCLC) is reported as 42.4 % in Japanese package insert. However, this efficacy data is based on clinical studies conducted in 1970s.This phase II study evaluated the efficacy and safety of IFM combination with recommended current supportive therapy for recurrent SCLC in second-line and heavily treated setting.

Methods Recurrent SCLC patients pretreated with one to three prior regimens received IFM monotherapy (1.5 g/m^2 for 3 days every 3weeks). Treatment was continued until disease progression or unacceptable toxicity. The primary end point was objective response rate.

Results Twelve patients were enrolled in the study from June 2009 to January 2013. The study was early terminated at interim analysis due to futility stop. Patient characteristics were as follows: median age was 65 years, 11 were males (91.7%) and eight (66.7%) and four (33.3%) were Performance Status 0 and 1, respectively. Four patients (33.3%) enrolled in second-line setting were all refractory relapse SCLC and 8 (66.7%) were heavily treated patients. No patient showed objective response. Stable disease was observed in 3 patients. Median progression-free survival and overall survival were 0.9 months (95% CI, 0.3–1.5) and 4.8 months (95% CI, 1.6–9.9), respectively. Although one grade 4 amylase increase possibly related to IFM was observed, toxicity profile was totally favorable.

Conclusions IFM monotherapy should not be used for refractory relapse or heavily treated SCLC, and no further investigation is required in these populations.

Clinical trial number UMIN Clinical Trials Registry with the identifier 000002465

Keywords Ifosfamide, Small cell lung cancer, Refractory relapse, Heavily treated

Introduction

Lung cancer is the leading cause of cancer-related deaths in the world, and approximately 15% of all lung cancer cases is small-cell lung cancer (SCLC) [1, 2]. SCLC is divided into limited disease (LD) or extensive disease (ED) on the basis of the Veterans' Administration Lung Study Group, and the majority of SCLC is ED at initial diagnosis. Despite the high sensitivity for first-line platinum-based therapies, a great portion of SCLC patients show relapse and the mortality rate of ED SCLC is approximately 95% within 2 years.

Treatment options for relapsed SCLC are still limited. For sensitive relapse SCLC (defined as relapse at an interval of ≥90 days after the completion of first-line therapy), topotecan monotherapy is the standard care as second-line chemotherapy [3, 4]. In addition, amrubicin or irinotecan are considered as treatment options based on the results of previous trials [5-8]. However, no definitive standard treatment has been established in patients with refractory relapse (defined as relapse at an interval of <90 days after the completion of first-line therapy). Furthermore, the benefit of third-line chemotherapy for SCLC remains unclear at all. Therefore, new promising treatment options for recurrent SCLC in second-line, or heavily treated setting are warranted.

Ifosfamide (IFM) is a chemotherapeutic alkylating agent related to nitrogen mustards. IFM is a pro-drug that is mainly metabolized by liver metabolic enzyme CYP3A4, and the activated metabolite disrupts the DNA composition of cancer cells for anti-tumor effect. IFM has shown favorable efficacy in various cancers, including prostate cancer, cervical cancer, intractable germ cell tumor, and pediatric malignant solid tumors [9-12]. In addition, the supportive strategies in decreasing serious toxicity of IFM were recently reported. First, encephalopathy was one of the dose-limiting toxicity which caused confusion in approximately 10–30% patients with IFM treatment; however, previous reports showed methylene blue was effective for the treatment of IFM-induced encephalopathy [13]. Second, supportive care consisted of mesna and extensive hydration could prevent hemorrhagic cystitis, which is the major adverse event of IFM [14].

In terms of evaluating the efficacy and safety of IFM for SCLC, the data from clinical trials conducted during the 1970–80s were available, in which the response rate of first-line IFM monotherapy was reported to 38.9–57% [15]. In the Japanese package insert of IFM, the response rate for SCLC is reported as 42.4% based on those 40-year old studies. However, it remains unclear about the true IFM efficacy for recurrent SCLC based on the RECIST criteria as well as the toxicity profile when used with newly supportive treatment such as prophylactic mesna, extensive hydration, and antiemetic serotonin antagonist. Moreover, IFM was known to easily penetrate to cerebrospinal

fluid, because its protein-binding rate was markedly lower than that in other anti-cancer agents. Since SCLC can rapidly spread to the brain and brain metastasis is directly related with prognosis, IFM might be a reasonable agent for SCLC, whereas the majority of anti-cancer agents were hardly delivered to cerebrospinal fluid due to blood–brain barrier [13].

Based on these observations, we conducted a phase II trial of IFM monotherapy with recommended supportive therapy in patients with previously treated SCLC and evaluated the efficacy and safety of this treatment strategy.

Materials and methods

Study design

This study is an open-label, single-arm phase II study conducted by two institutions (Nagoya University Hospital and Japanese Red Cross Nagoya Daiichi Hospital) in Japan. The study was registered in the UMIN Clinical Trials Registry with the identifier 000002465 and performed in accordance with the principles laid out in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of each center. The primary endpoint was the objective response rate (ORR) and the secondary endpoints were the progression-free survival (PFS), overall survival (OS), and safety.

Patient eligibility

The major eligibility criteria of the study were as follows: (1) pathologically confirmed diagnosis of SCLC, and either relapse type (sensitive relapse and refractory relapse) was eligible; (2) age ≥20 and ≤75 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2; (4) history of one to three prior chemotherapeutic regimens; (5) at least one measurable lesion defined as Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1); and (6) adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥ 1500/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin value > 9 g/dL, bilirubin level ≤ 1.5 mg/dL, aspartate transaminase level ≤ 100 mg/dL, alanine transaminase level ≤ 100 mg/dL, and creatinine level ≤ 1.5 mg/dL). The key exclusion criteria were as follows: (1) patients with uncontrolled massive pleural or pericardial effusion; (2) symptomatic brain metastases; (3) patients with supra vena cava syndrome; and (4) patients with severe comorbidity (severe cardiac disease such as myocardial infarction, angina pectoris within the last 6 months or cerebrovascular disease within the last 6 months, or uncontrolled hypertension/active infection)

Treatment

Treatment schedule are shown in Table 1. Patients received IFM (1.5g/m^2/day for 3 days) and mesna (900 mg / m^2 / day for 3 days) every 3 weeks. Prophylactic serotonin

receptor antagonists were routinely used. This treatment schedule was continued until disease progression or development of unacceptable toxicity. The next cycle of IFM was initiated when the following criteria were fulfilled: leukocyte count was ≥3000/mm^3, platelet count ≥75,000/mm^3, and no diarrhea was observed. The dosage of IFM was reduced to 80% of the initial dosage when grade 4 leukopenia and/or neutropenia, nadir platelet count <20,000/mm^3, ≥grade2 diarrhea, or ≥grade 3 non-hematological toxicity except nausea, vomiting, appetite loss, general fatigue, and alopecia were observed on the previous course. Secondary dose reduction was not allowed and the protocol was discontinued.

Efficiency and safety evaluation

Pre-treatment investigations included a complete medical history and physical examination, chest radiography, computed tomography (CT) of the chest and abdomen, brain CT or magnetic resonance imaging (MRI), and radionuclide bone scan. Chest radiography was performed for every cycle, and the chest CT was enforced every two cycles. Tumor response was assessed in accordance with RECIST, version 1.1. PFS was defined as the time from the date of study enrollment until the date of observed progressive disease (PD) or death due to any cause or the date of the last follow‐ up. OS was defined as the time from the date of study enrollment until death due to any cause or the date of last follow‐ up. Safety was assessed by using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

This study was designed as a phase II trial based on Simon's two-stage minimax designs. The sample size was calculated from an expected response rate of 25% and a minimum of 5% with one-sided α of 0.05 and β of 0.2. The estimated sample size was 16 and we determine the optimal target sample size for 20, to allow for dropouts. At interim analysis, one PR in 12 patients was required for going to the next stage of the trial. If two or more PR were observed in 16 patients, the regimen was considered as a promising treatment for recurrent SCLC. The expected response rate and minimum response rate was based on the ORR of amrubicin and topotecan monotherapy in patients with previously treated SCLC, which was reported as 21–52% and 7–24% [4-7, 16, 17]. All analyses were conducted by using the intention-to-treat principle. Time-to-event endpoints were analyzed by using the Kaplan–Meier analysis method and all data analyses were conducted by using statistical JMP software, version 10.0.0. (SAS Institute Inc., USA).

Results

Patient characteristics

Between April 2009 and February 2013, 12 patients were included in this study. The study was early terminated by the interim analysis based on the criteria for futility stop.

Patient characteristics are listed in Table 2. Median age was 65 years (range, 45–73), 11 patients (91.7%) were male, and eight and four patients were PS 0 (66.7%) and PS 1 (33.3%), respectively. Among the 12 patients, 4 patients (33.3%) received IFM chemotherapy in second-line setting, 6 (50%) in third-line, and 2 (16.7%) in fourth-line, respectively. All 4 patients treated with IFM in second-line setting were refractory relapse SCLC. In patients who received two or three prior chemotherapy, amrubicin and irinotecan monotherapy were the commonly used regimen after platinum-based first-line therapy. The median number of IFM cycles administered was 2 (range, 1-4). The reasons for discontinuation of IFM were disease progression in 11 (91.7%) patients and unacceptable toxicity in one (8.3%) patient.

Efficiency

No complete response (CR) and partial response (PR) was observed in 12 patients and the ORR was 0%. Stable disease (SD) was confirmed in 3 patients and disease control rate was 25% (95% CI, 5.5–57.2%; Table 3). At the time of data cut-off, disease progression and death were observed in 12 (100%) and 11 patients (91.7%), respectively. The median PFS was 0.9 months (95% CI, 0.3–1.5 months; Fig. 1A). Median OS was 5.8 months (95% CI, 1.6–9.9 months; Fig. 1B).

Safety

The safety profile is shown in Table 4. No treatment-related death was observed in this study. In terms of hematological toxicity, one patient (8.3%) had grade 3 leukopenia and two patients (16.7%) had grade 1–2 anemia. The comparison between basic line and hematopenia at nadir was shown in Fig. 2.

As for non-hematological toxicity, grade 3 hyponatremia were observed in 2 patients. One patient developed grade 4 amylase increase leading to termination of IFM. The patient had no comorbidity that could be associated with amylase increase; thus, we judged this severe adverse event as possibly related to IFM treatment. However, the patient promptly recovered upon discontinuation of IFM. In addition, one patient experienced grade 3 pulmonary edema due to fluid replacement during IFM chemotherapy. This patient also recovered to their previous condition after the discontinuation of IFM. No encephalopathy or hemorrhagic cystitis was observed in the study.

Discussion

To the best of our knowledge, this was the first study that evaluated the efficacy and safety of IFM monotherapy with the recommended supportive care for hemorrhagic

cystitis and emesis in patients with recurrent SCLC. The study resulted in futility stop at interim analysis. Based on our prospective evaluation, IFM monotherapy had no activity for recurrent SCLC.

The treatment strategy based on driver oncogenes, such as EGFR or EML4-ALK, has developed in non-small cell lung cancer (NSCLC) in the last decade [18-20]. However, no molecular targeted therapies have shown survival benefit in SCLC to date despite several clinical studies with bevacizumab or sunitinib [21, 22]. When we reviewed the development of new standard treatment in hematological malignancy, arsenic trioxide, an old agent reported to have an anti-leukemic effect in 19th century, showed clinical benefit in patients with acute promyelocytic leukemia in a well-designed, recent, prospective, randomized clinical trial[23]. To improve the prognosis of SCLC, it is rightfully important to develop new agents targeting SCLC. In addition to these efforts, it would be beneficial to examine the possibility of re-evaluating old or existing anticancer agents not fully investigated like our current study, though resulted in negative results.

In our study, IFM showed disappointing results in patients with refractory relapse or heavily treated SCLC. Few prospective clinical trials were conducted in patients with heavily treated SCLC, which is considered as the population of unmet medical needs. Therefore, we have no choice but to decide to try the possibly effective agents or selecting best supportive care for this specific population. In the view of this current status, the negative results of our study would provide useful information regarding the clinical decision, especially in heavily treated settings.

The hematological toxicity herein was markedly less frequent compared with the historical data of amrubicin, irinotecan, and topotecan. In addition, no encephalopathy and hemorrhagic cystitis previously reported in 1970–80’s trials were observed although the sample size of our study was small. Although one grade 4 amylase increase possibly related to IFM was observed, the patient promptly recovered after discontinuation of IFM. Collectively, IFM showed favorable toxicity profile in our study, which might come from pre-planned supportive treatment of the study.

Our study had several limitations. First, because of early termination, sample size was small. Second, we could not obtain the efficacy of second-line IFM for sensitive relapse SCLC in second-line setting because the enrolled patients with one prior therapy were all refractory relapse. Based on the favorable toxicity profile of IFM in our study and previous evidences regarding combination therapy including IFM, doublet or triplet therapy including IFM for sensitive relapse SCLC might have some worthy to evaluate in future clinical trial.

In conclusion, this study was early terminated due to futility stop at interim

analysis, although toxicity profile was favorable. Based on our clinical observations, we conclude that IFM monotherapy should not be used for refractory relapse or heavily treated SCLC, and no further investigation is required in these populations.

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Figure legends

Fig. 1

Kaplan–Meier plots showing (A) progression-free survival (PFS), and (B) overall survival (OS).

Fig. 2

The comparison between basic line and hematopenia at nadir (A) White blood cell (WBC) counts, (B) neutrophilic leukocyte (neutro) counts, (C) hemoglobin (Hb), and (D) blood platelet (Plt) counts were indicated, respectively.

Table 1. Treatment schedule

	Dose	Schedule	
Ifosfamide	1.5 g/m^2	Days 1–3	q3–4 week
Mesna	900 mg/m^2	Days 1–3	

Table 2. Patient Characteristics (n = 12)

		Number of patients (%)	
Age, median (range)		65	(45–73)
Sex			
	Male	10	(92)
	Female	2	(8)
ECOG PS			
	0	8	(67)
	1	4	(33)
Stage at initial diagnosis			
	limited disease	4	(33)
	extensive disease	8	(67)
Type of relapse			
	refractory relapse	12	(100)
	sensitive relapse	0	(0)
Stage at starting IFM therapy			
	limited disease	4	(33)
	extensive disease	8	(67)
Number of prior treatment			
	1	4	(33)
	2	6	(50)
	3	2	(17)
TRT			
	(+)	3	(25)
	(-)	9	(75)
PCI			
	(+)	3	(25)
	(-)	9	(75)

ECOG PS, Eastern cooperative oncology group performance status; IFM, ifosfamide; PCI: prophylactic cranial irradiation, TRT: thoracic radiation therapy

Table 3. Summary of efficacy with tumor response

	n	(%)
CR	0	0
PR	0	0
SD	3	25
PD	9	75
NE	0	0
ORR		0%
DCR		25%
(95% CI)		(5.5%-57.2%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate CI, confidence interval

Table 4. Safety profile

	Grade				Grade 3/4
	1	2	3	4	% of Patients
Hematologic					
Leukopenia	2	1	1	0	8.3
Anemia	1	1	0	0	0
Thrombocytopenia	2	0	0	0	0
Non-hematologic					
Encephalopathy	0	0	0	0	0
AST increase	1	0	0	0	0
Creatinine increase	0	0	0	0	0
Hematuria	0	0	0	0	0
Hyponatremia	3	0	2	0	16.7
AMY increase	0	0	0	1	8.3
Infusion reaction	0	0	0	0	0
Dermatitis	0	0	0	0	0
Congestive heart failure	0	0	0	0	0
Lung edema	0	0	1	0	8.3
Interstitial pneumonitis	0	0	0	0	0
Constipation	3	0	0	0	0
Diarrhea	2	0	0	0	0
Anorexia	5	0	0	0	0
Nausea/Vomiting	5	0	0	0	0

AST, aspartate transaminase, AMY, amylase; ILD, interstitial lung disease

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Fig. 1

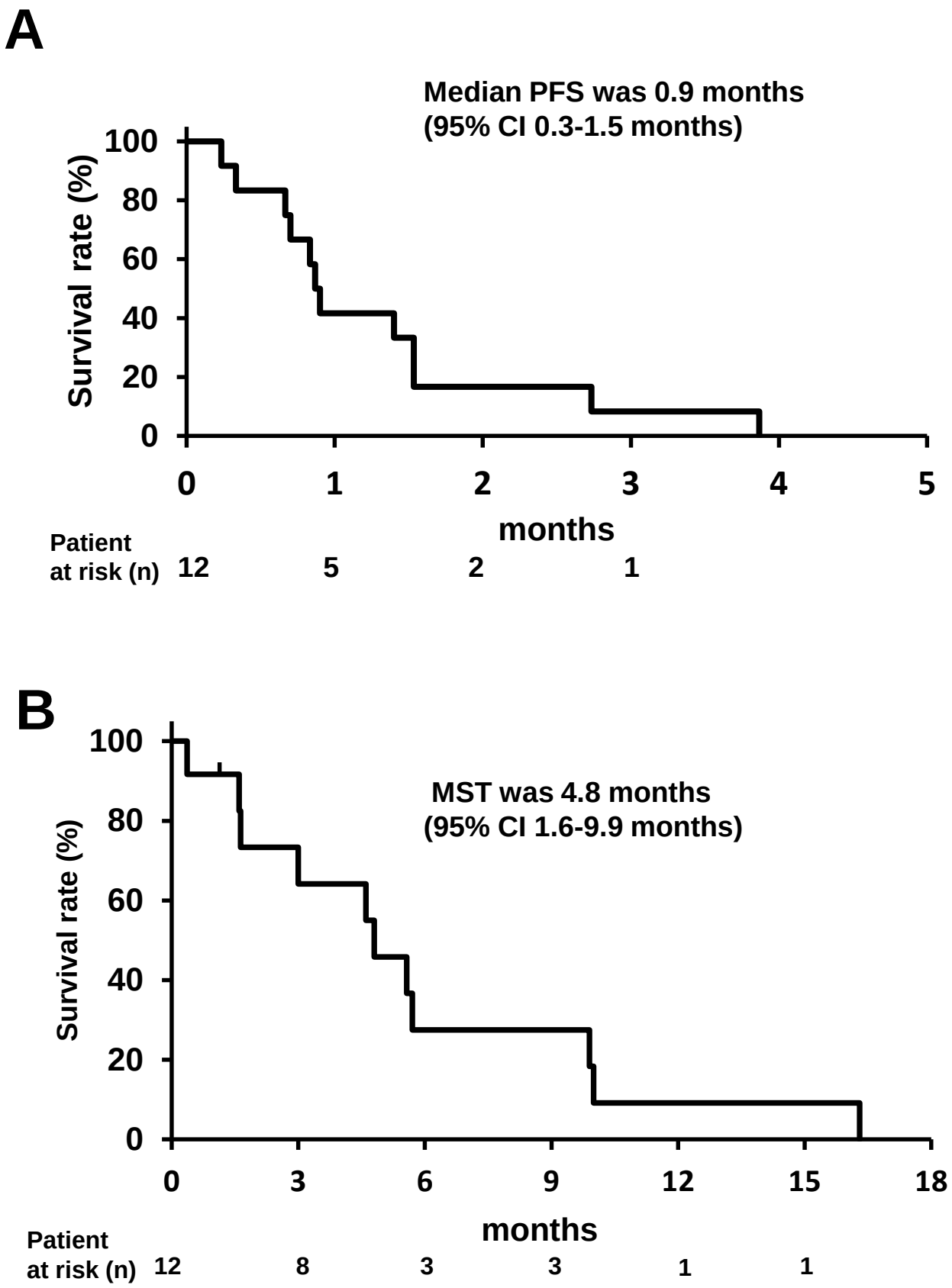

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Fig. 2