Table 4. Gender differences in the increase of serum creatinine levels and toxicity grades during the first and all cycles of chemotherapy

	Females (n = 149)	Males (n = 468)	P-value
	N (%)	N (%)	
During the first cycle of chemotherapy			
An increase in CRN (mg/dL)			
0–0.3	130 (87.2)	350 (74.8)	0.006
0.4–0.6	13 (8.7)	73 (15.6)	
≥0.7	6 (4.0)	45 (9.6)	
Median (range)	0.20 (0–1.2)	0.20 (0–3.6)	<0.001
CTC-AE grade			
0	83 (55.7)	336 (71.8)	0.001
1	51 (34.2)	105 (22.4)	
2–3	15 (10.1)	27 (5.8)	
During all cycles of chemotherapy			
An increase in CRN (mg/dL)			
0–0.3	101 (67.8)	222 (47.4)	0.001
0.4–0.6	31 (20.8)	125 (26.7)	
≥0.7	17 (11.4)	121 (25.9)	
Median (range)	0.20 (0–1.8)	0.40 (0–3.6)	<0.001
CTC-AE grade			
0	54 (36.2)	228 (48.7)	0.023
1	63 (42.3)	168 (35.9)	
2–3	32 (21.5)	72 (15.4)	

CTC-AE, Common Toxicity Criteria–Adverse Event ver. 3.0.

relatively low volume of hydration in male patients, because the infusion volume administered was the same in male and female patients despite the larger physique of male patients. However, the explanation attributed to this small difference in the infusion volume might not be plausible, because the volume of hydration was not clearly associated with cisplatin-induced renal toxicity in a previous study.[8]

Because this study has suggested that generic cisplatin might be slightly more toxic to the kidneys, some kind of countermeasures are necessary. First, the content of hydration and timing of mannitol administration should be reconsidered to avoid renal toxicity. We had not included magnesium in the hydration fluid, but recent randomized trials showed that addition of magnesium was effective in reducing cisplatin-induced renal toxicity.[10,11] We have administered mannitol after cisplatin infusion, but the National Cancer Center Hospital (NCCH) guideline recommends using mannitol before cisplatin infusion. If these countermeasures fail to reduce renal toxicity, then the use of generic cisplatin would not be recommended.

A major limitation of the present study is that the generic and innovator cisplatin formulations were not allocated in a randomized fashion to the study population, but was determined by the period of the treatment. Although cisplatin administration in our hospital was consistent throughout the study period, there might be unknown factors associated with renal toxicity influenced by the study period.

Generic formulations are approved without clinical trials in Japan, as well as in other countries. This system has worked well to reduce drug costs safely, provided that the drug has a potentially low toxicity profile. However, the results of this study suggest that more attention should be given to the developmental system of generic formulations, especially in relation to anticancer agents, which might have severe and life-threatening toxicities. One possibility is disclosure of the drug manufacturing process so that drug companies can strictly follow the process when they develop a generic formulation of the original drug. Utmost importance should also be given to postmarketing surveys. A survey of at least 1000 treated patients can define the toxicity profile of a new formulation. These revisions of the developmental process might offer safer generic formulations to patients without further increase of the medical costs.

In conclusion, renal toxicity was slightly more severe in patients treated with a generic cisplatin formulation than in those treated with an innovator formulation, especially among male patients. This result suggests that more attention should be given to the developmental system of generic formulations, especially in those drugs that have a narrow therapeutic window, such as anticancer agents.

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Disclosure Statement

The authors indicate no potential conflict of interest.

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Short Communication

Clinical Implication of the Antidiuretic Hormone (ADH) Receptor Antagonist Mozavaptan Hydrochloride in Patients with Ectopic ADH Syndrome

Ectopic ADH Syndrome Therapeutic Research Group, Ken Yamaguchi[1,*], Noriharu Shijubo[2], Tetsuro Kodama[3], Kiyoshi Mori[3], Takahiko Sugiura[4], Takayuki Kuriyama[5], Masaaki Kawahara[6], Tetsu Shinkai[7], Haruo Iguchi[7] and Masanori Sakurai[8]

[1]Shizuoka Cancer Center, Shizuoka, [2]Department of Respiratory Medicine, JR Sapporo Hospital, Sapporo, [3]Department of Medical Oncology, Division of Thoracic Oncology, Tochigi Cancer Center Hospital, Tochigi, [4]Department of Medical Oncology, Daido Hospital, Nagoya, [5]Department of Internal Medicine, Kuriyama Clinic, Tanabe, [6]Department of Respiratory Diseases, Otemae Hospital, Osaka, [7]Shikoku Cancer Center, Matsuyama and [8]Department of Internal Medicine, Mizuno Hospital, Tokyo, Japan

*For reprints and all correspondence: Ken Yamaguchi, Office of the President, Shizuoka Cancer Center, Shimonagakubo 1007, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan. E-mail: k.yamaguchi@scchr.jp

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Ectopic antidiuretic hormone syndrome is a medical emergency characterized by dilutional hyponatremia. Clinical effectiveness of the vasopressin V2 receptor antagonist mozavaptan was evaluated in 16 patients. In short-term (7-day) treatment with the drug, serum sodium concentration (mean ± standard deviation) significantly ($P = 0.002$) increased from 122.8 ± 6.7 to 133.3 ± 8.3 mEq/l, and symptoms due to hyponatremia were improved. On the basis of these results, mozavaptan (Physuline®) was approved as an orphan drug for the treatment of the syndrome in 2006 in Japan. During the 43 months following its launch, 100 patients have been treated with the drug; overall clinical effects of the drug were found similar to those of this clinical trial. Clinically, mozavaptan may allow hyponatremic patients to be treated by aggressive cancer chemotherapy with platinum-containing drugs. Moreover, the drug may free patients from strict fluid-intake restrictions and thereby improve their quality of life.

Key words: SIADH – ectopic ADH syndrome – small cell lung carcinoma – hyponatremia – antagonist

INTRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is divided into two categories; one is the ectopic ADH syndrome induced by abnormally secreted ADH (arginine vasopressin) from cancer cells, and another is the morbidity caused by inappropriately secreted ADH from the pituitary gland in various benign diseases. In both situations of SIADH, ADH binds to vasopressin V2 receptors (V2Rs) in renal tubules and thereby increasing water reabsorption. Clinically, SIADH is characterized by elevated fluid retention in the body, resulting in dilutional hyponatremia and subsequent manifestations of various central nervous system (CNS) symptoms.

In the present study, clinical effectiveness of a newly developed vasopressin V2R antagonist was evaluated in patients with ectopic ADH syndrome. This morbidity is frequently observed in patients with small cell lung carcinoma (SCLC) and makes it to be difficult to aggressive cancer chemotherapy with platinum-containing drugs. Patients with SIADH often require severe water restriction, worsening their quality of life.

Mozavaptan, the world's first non-peptide V2R antagonist with aquaretic action, was developed by Otsuka Pharmaceutical, Japan, in 1989 (1). Its potent effect was first demonstrated by clinical pharmacological trials involving healthy adult male subjects in 1992 (2). To understand

whether mozavaptan might play an important role in the treatment of ectopic ADH syndrome, the Ectopic ADH Syndrome Therapeutic Research Group conducted an open-label multicenter clinical trial at Japanese hospitals from December 1994 to December 1997. This paper describes the study results and their implication for mozavaptan's potential usefulness in the treatment of cancer-related ectopic ADH syndrome.

PATIENTS AND METHODS

This open-label, multicenter study protocol was approved by the Institutional Review Board of each participating medical institution prior to its inception; written informed consent was obtained from all patients.

Recruited were inpatients aged 20 to <75 years who had malignant tumors that might cause ectopic ADH syndrome as well as the diagnostic criteria of ectopic ADH syndrome as defined by Bartter and Schwartz (3) such as serum sodium concentration ≤124 mEq/l, persistent urinary sodium excretion, normal renal, adrenal, and thyroid function, and no evidence of edema or dehydration.

Following a ≤2-day placebo administration period during which baseline data were collected, patients were given orally mozavaptan (single 30 mg tablet) once daily for 7 days, or where this was difficult, 3 days was allowed. Fluid restriction was used throughout the study period only for patients in whom it had already begun. Treatment of hyponatremia with demeclocycline, lithium chloride, or urea was not permitted.

The primary endpoint was serum sodium concentration. Blood samples were collected immediately before dosing on each test day. Clinical symptoms associated with hyponatremia such as anorexia, nausea/vomiting, headache, and CNS symptoms were recorded. Urine volume, urinary osmolality, urinary electrolyte (sodium, potassium, chloride) excretion, serum electrolyte (potassium, chloride) concentration, serum osmolality, and plasma ADH concentration were measured. New medical problems or exacerbations of those already existing were reported as adverse events.

In each case, the serum sodium level after the final administration of the study drug was compared with baseline value. The patients are divided into three groups: (i) the serum sodium level is improved to normal range; (ii) the level is still low, but increase is ≥6 mEq/l and (iii) the level is still low, and increase is <6 mEq/l. And mean sodium concentration after the final administration of the study drug was compared with that of baseline value by paired *t*-test.

RESULTS

Sixteen patients [M/F: 10/6; mean age: 63.9 (range: 48–78) years] who received at least one dose of the study drug were included in the efficacy and safety evaluation. All patients received mozavaptan 30 mg once daily for 7 days, except two individuals who received treatment for 3 days.

Underlying diseases were SCLC ($n = 14$), thymic small cell carcinoma ($n = 1$) and cervical cancer ($n = 1$). Fluid intake was restricted in 5 of the 16 patients (Table 1).

Serum sodium concentration (mean ± SD) at the time of diagnosis of the ectopic ADH syndrome was 117.3 ± 4.3 (range: 110–124) mEq/l. Plasma ADH concentration was 4.9 ± 5.8 (median: 2.3; range: 0.4–18.9) pg/ml immediately before treatment.

At baseline and at the end of study, mean serum sodium concentration was 122.8 ± 6.7 and 133.3 ± 8.3 mEq/l, respectively, a statistically significant difference ($P = 0.002$; Fig. 1). Serum sodium concentration increased at 24 h after the first administration of mozavaptan and remained elevated ≤24 h after administration for 7 days. Serum osmolality gradually increased starting from 24 h after first administration till the study end. Cumulative urine volume over 24 h increased on the first treatment day, whereas urine osmolality decreased in the first two treatment days.

A total of 16 patients were evaluated for the serum sodium level. The serum sodium level was improved to normal range in eight patients, still below normal range but increased by at least 6 mEq/l in four patients and increased by <6 mEq/l in four patients (Table 1).

Symptoms associated with ectopic ADH syndrome such as anorexia, nausea/vomiting, headache and CNS symptoms improved or disappeared in seven of eight patients who had at least one of these symptoms at baseline. By symptom, anorexia disappeared in three and improved in two among eight patients who had the symptom at baseline, whereas nausea/vomiting, headache and CNS symptoms disappeared by the completion of treatment in all patients who had at least one of the symptoms at baseline. On the other hand, however, new anorexia and headache developed in one patient each.

Although some patients showed slight increases or decreases of plasma ADH concentration after receiving mozavaptan, overall there were no obvious changes.

There were 35 adverse events in 11 of the 16 patients; none was serious. The most common adverse event was dry mouth developing in five patients. Fifteen adverse drug reactions occurred in six patients (dry mouth, $n = 5$; increased blood potassium, $n = 2$; malaise, increased AST, increased ALT, decreased blood calcium, increased blood lactate dehydrogenase, increased blood urea, decreased appetite and nocturia, $n = 1$ each).

One patient was withdrawn after administration of the study drug for 3 days because of anorexia. After completion of administration of mozavaptan, one cancer-related death occurred 30 days post-treatment (ID 1 in Table 1); the patient had small cell lung cancer, and had myasthenia gravis, diabetes, pneumonia and hypertension. Chemotherapy (carboplatin and etoposide) was given from 146 to 144 days before treatment with mozavaptan, which reduced the tumor size and improved SIADH. However, the chemotherapy was

Table 1. Clinical characteristics of each patient at baseline and changes in serum sodium concentration/clinical symptoms

ID	Sex (M/F)	Age (years)	Disease	Tx duration (days)	Fluid-intake restriction	Data at baseline			Changes in serum sodium concentration (mEq/l)				Clinical symptoms
						Plasma ADH concentration (pg/ml)	Serum osmolality (mOsm/kg)	Urine osmolality (mOsm/kg)	At the time of diagnosis	At baseline	24 h after the first administration	24 h after the last administration	
1	F	64	SCLC	7	Yes	12.5	274	712	115	129	136	139	ANRX improved, NV disappeared, HA disappeared
2	F	64	Thymic SCC	3	Yes	3.3	256	—	110	122	133	140	ANRX improved, NV disappeared, HA disappeared, CNSS disappeared
3	M	54	SCLC	7	Yes	0.8	254	754	115	123	130	139	ANRX disappeared, HA disappeared, CNSS disappeared
4	M	76	SCLC	7	No	2.1	254	657	119	111	121	119	ANRX disappeared, NV disappeared
5	M	65	SCLC	3	Yes	2.4	300	753	121	130	134	142	ANRX developed
6	M	66	SCLC	7	No	18.9	256	461	119	123	—	128	None
7	M	78	SCLC	7	No	0.5	279	590	124	127	128	133	None
8	F	75	SCLC	7	No	0.4	254	465	124	120	125	122	None
9	M	66	SCLC	7	No	7.8	261	492	115	117	123	127	ANRX continued, NV disappeared, HA developed
10	M	48	SCLC	7	Yes	2.1	283	730	110	132	129	127	None
11	M	66	SCLC	7	No	1.4	241	450	116	107	117	130	ANRX disappeared, NV disappeared, HA disappeared, CNSS disappeared
12	F	53	SCLC	7	No	1.5	241	465	117	127	138	148	n/a
13	F	60	SCLC	7	No	2.8	245	406	123	122	128	142	None
14	M	65	SCLC	7	No	5.2	263	370	114	123	130	139	None
15	M	63	SCLC	7	No	15.7	275	755	116	129	133	133	ANRX continued
16	F	60	Cervical cancer	7	No	1.0	268	349	119	123	132	140	ANRX continued, HA disappeared, CNSS disappeared

SCLC, small cell lung carcinoma; Thymic SCC, thymic small cell carcinoma; ANRX, anorexia; NV, nausea/vomiting; HA, headache; CNSS, central nervous system symptom; n/a, not available.

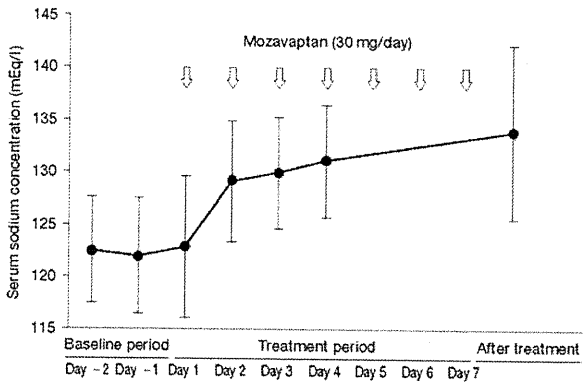

Figure 1. Time-course of serum sodium concentration (mean ± SD) in 16 cancer patients with ectopic ADH syndrome. Baseline serum sodium concentration was 122.8 ± 6.7 mEq/l. At 24 h after the first dose, serum sodium increased to 129.1 ± 5.7 mEq/l; at 24 h after completion of treatment, the value was 133.3 ± 8.3 mEq/l.

terminated due to marked myelosuppression, and then this led to marked tumor growth. The serum sodium concentration was 132 mEq/l 29 days before the mozavaptan treatment, but gradually decreased to 119 mEq/l 14 days before treatment. At that time, the patient's condition did not permit chemotherapy, and mozavaptan therapy was performed. Although mozavaptan was effective, the condition became worse due to rapid tumor progression. The patient died 30 days after completion of the mozavaptan therapy, and the autopsy demonstrated direct invasion to heart and thoracic vertebra, indicating that the patient had died of cancer. No other serious adverse events were reported.

DISCUSSION

Since the ectopic ADH syndrome is the morbidity induced by inappropriately secreted ADH from cancer cells, V2R antagonist rationally might be expected to exert pharmacological effects in the syndrome. During Phase I pharmacological evaluation, mozavaptan 30 mg/day exerted potent V2R antagonistic activity. Therefore, we plan to evaluate the clinical efficacy and safety of this agent at a dose of 30 mg/day in cancer patients with ectopic ADH syndrome defined by Bartter and Schwartz (3).

We found that the drug increased the mean serum sodium level; 10 patients at 24 h after the first dose and 12 patients at 24 h after the last dose showed a ≥6 mEq/l increase in serum sodium concentration from baseline.

Of 12 patients who showed an increase in serum sodium concentration of ≥6 mEq/l from baseline at 24 h after the last dose, 7 had anorexia, nausea/vomiting, headache and/or CNS symptoms before treatment. Anorexia ($n = 7$) disappeared in three, was alleviated in two and remained unchanged in two patients; all other symptoms (nausea/vomiting in five, headache in five and CNS symptoms in four patients) disappeared following therapy. However, new anorexia and headache developed in one patient each. Of the remaining four subjects who showed an increase in serum sodium concentration of <6 mEq/l, three had no symptoms and one complained of anorexia that remained unchanged 24 h after the last dose.

Since SCLC is the chemo-sensitive tumor and SIADH is the condition of oncologic emergency, urgent treatment is always required. However, in the cases of SIADH, hyponatremia makes it difficult to perform chemotherapy; hydration is necessary for the therapy with cisplatin-based chemotherapy. Mozavaptan improved compliance to chemotherapy in patients with ectopic ADH syndrome.

The present study did not plan to give chemotherapy during the study period. Thus, information on chemotherapy was not designed to be collected from patients. However, we evaluated present cases whether they received chemotherapy after the mozavaptan treatment. Information was obtained from 14 patients of the 16 subjects, 9 were administered mozavaptan prior to scheduled chemotherapy, and 8 of these underwent chemotherapy with the regimen including cisplatin or carboplatin after successful correction of hyponatremia.

With regard to safety, the treatment was discontinued in one patient due to adverse drug reaction, and two patients required treatment for adverse effects but recovered after appropriate treatment. There was no excessively rapid increase in serum sodium concentration or central pontine myelinolysis, suggesting that mozavaptan can be safely used in the target patient population.

On the basis of these results, mozavaptan (Physuline®) was approved in Japan as an orphan drug for the treatment of ectopic ADH syndrome, in 2006. It is worth noting that until now demeclocycline, lithium chloride or urea was reported effective for the ectopic ADH syndrome, although clinical experiences revealed that the effects of these drugs are limited (4).

In the USA and EU, there are two V2R antagonists available on the market—conivaptan (injection formulation) (5) and tolvaptan (oral tablet) (6). Conivaptan, a dual V1a receptor and V2R antagonist, is marketed in the USA with the indication of 'treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients'. Tolvaptan, which by structural modification has a higher affinity for the V2R than does its parent drug, mozavaptan, is marketed in the USA with the indication of 'treatment of clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure, cirrhosis and SIADH' and in the EU with the indication of 'treatment of adult patients with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)'. Mozavaptan is currently the only approved drug available for treatment of patients with ectopic ADH syndrome (7) in Japan but is neither approved nor under development outside Japan.

During the 43 months following its launch, 100 patients have been treated with the drug. On the basis of the post-marketing drug use results survey, overall clinical effects of the drug have been found similar to those of the

clinical trial. Mozavaptan provides two important contributions for the treatment of ectopic ADH syndrome. First, short-term treatment with mozavaptan may allow hyponatremic patients who might otherwise be contraindicated to receive aggressive cancer chemotherapy with platinum-containing drugs. Second, mozavaptan may free patients from strict fluid-intake restrictions and thereby improve their quality of life. Thus, mozavaptan provides new treatment options for aggressive chemotherapy as well as for palliative care in patients with ectopic ADH syndrome.

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Conflict of interest statement

None declared.

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Appendix

Ectopic ADH Syndrome Therapeutic Research Group (continued).

Shosaku Abe: Sapporo Minamisanjo Hospital.

Yutaka Nishiwaki and Koichi Goto: Division of Thoracic Oncology, National Cancer Center Hospital East.

Kimihide Yoshida and Toyoaki Hida: Department of Thoracic Oncology, Aichi Cancer Center Hospital.

Hideki Muramatsu: Department of Respiratory Diseases, Kainan Hospital.

Kunihiko Gotoh: Gotoh Clinic of Internal Medicine.

Koichiro Tatsumi: Department of Respirology, Graduate School of Medicine, Chiba University.

Shinji Atagi: Department of Internal Medicine, National Hospital Organization Kinki, Chuo Chest Medical Center.

Toshihiko Nishian: Nishian Clinic.

Toshio Tabei: Division of Breast Surgery, Saitama Cancer Center.

Koji Sato: Niigata Association of Occupational Health, Inc.

Ichiro Kawase: Osaka Prefectural Medical Center for Respiratory and Allergic Disease.

Saburo Sone: Department of Respiratory Medicine and Rheumatology, Institute of Health Biosciences, The University of Tokushima Graduate School.

Eiji Shimizu: Division of Medical Oncology and Molecular Respirology, Faculty of Medicine, Tottori University.

Jiro Takahara: Department of Internal Medicine, Uchinomi Hospital.

Jiro Fujita: 1st Department of Internal Medicine, University of the Ryukyus Hospital.

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ORIGINAL ARTICLE

Pharmacokinetics of aprepitant and dexamethasone after administration of chemotherapeutic agents and effects of plasma substance P concentration on chemotherapy-induced nausea and vomiting in Japanese cancer patients

Toshiaki Takahashi · Yukiko Nakamura · Asuka Tsuya · Haruyasu Murakami · Masahiro Endo · Nobuyuki Yamamoto

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Abstract
Purpose This study was conducted to determine the pharmacokinetics of aprepitant and dexamethasone as well as the relationship between the plasma concentration of substance P and nausea/vomiting in Japanese cancer patients.
Methods After administration of aprepitant (125/80 mg group [10 patients]: 125 mg on day 1 and 80 mg on days 2–5; 40/25 mg group [10 patients]: 40 mg on day 1 and 25 mg on days 2–5) and dexamethasone (6 mg on day 1 and 4 mg on days 2 and 3 in the 125/80 mg group, and 8 mg on day 1 and 6 mg on days 2 and 3 in the 40/25 mg group) to Japanese cancer patients receiving at least moderately emetogenic antitumor agents, the plasma concentrations of aprepitant, dexamethasone, and substance P were measured.
Results All of 20 patients were treated with the highly emetogenic agent cisplatin (≥70 mg/m^2). The C_{max} and $AUC_{0-24\ h}$ of aprepitant in Japanese cancer patients were similar with those in non-Japanese patients. The clearance of dexamethasone in the 125/80 mg group was approximately one-half of that previously determined in the absence of aprepitant. The substance P concentration in plasma significantly increased only in patients with delayed nausea/vomiting.
Conclusions This study demonstrated similar plasma pharmacokinetics of aprepitant in Japanese and non-Japanese, the validity of reducing dexamethasone dose, and the existence of increased plasma substance P concentration in patients receiving highly emetogenic cisplatin-based chemotherapy.

Keywords Aprepitant · Dexamethasone · Substance P · Pharmacokinetics · Chemotherapy-induced nausea and vomiting

Introduction

Aprepitant is a neurokinin-1 (NK_1) receptor antagonist developed as a treatment for both acute and delayed chemotherapy-induced nausea and vomiting (CINV). It has a novel mechanism of action (i.e., by inhibiting the binding of substance P to the NK_1 receptor in the vomiting center) [1–3]. In the guidelines for management of CINV, aprepitant is recommended to be used in combination with a serotonin antagonist and dexamethasone to prevent nausea/vomiting induced by highly and moderately emetogenic cancer chemotherapy [4–6].

Although aprepitant has no effect on the pharmacokinetics of serotonin antagonists (ondansetron, granisetron, palonosetron) [7, 8], aprepitant inhibits CYP3A4 and in turn inhibits the metabolism of dexamethasone, a substrate of CYP3A4 [9]. It has been shown that the area under the concentration–time curve (AUC) of dexamethasone is increased approximately two times after administration of aprepitant at a dose of 125 mg on day 1 and at a dose of 80 mg on days 2–5 in healthy adults, and so, to maintain

T. Takahashi (✉) · Y. Nakamura · A. Tsuya · H. Murakami · N. Yamamoto
Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: t.takahashi@scchr.jp

M. Endo
Division of Diagnostic Radiology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

dexamethasone at the prescribed blood level in the presence of aprepitant, the dose of dexamethasone has to be reduced by 50% [9]. Although a previous population pharmacokinetic study of dexamethasone combined with aprepitant supported the validity of this dose reduction of dexamethasone [10], there has been no full pharmacokinetic study of dexamethasone and aprepitant in cancer patients who receive emetogenic cancer chemotherapy.

While aprepitant may have an antiemetic effect by inhibiting the binding of substance P to the NK_1 receptor in the vomiting center as mentioned above, it is still unclear whether there is any change in the in vivo kinetics of substance P after administration of chemotherapeutic agents, or how the in vivo kinetics of substance P is related to CINV.

This study was conducted to determine the pharmacokinetics of aprepitant as well as dexamethasone in Japanese cancer patients and to verify the dose reduction of dexamethasone used in combination with aprepitant, and furthermore, to evaluate the relationship between CINV and in vivo kinetics of substance P after administration of chemotherapeutic agents.

Patients and methods

Inclusion criteria

Japanese cancer patients aged between 20 and 74 years who received cancer chemotherapy were included in this study. Cancer chemotherapy consisted of at least moderately (Hesketh level ≥ 3 [11]) emetogenic chemotherapeutic agents on day 1 only. With a performance status of 0–2 and an estimated life expectancy of at least 3 months, patients met the following laboratory criteria: white blood cell count $\geq 3{,}000/mm^3$ and neutrophil count $\geq 1{,}500/mm^3$; platelet count $\geq 100{,}000/mm^3$; AST (GOT) and ALT (GPT) $\leq 1.5 \times$ upper limit of the normal range at the facility; ALP $\leq 2.5 \times$ upper limit of the normal range at the facility; total bilirubin ≤ 1.5 mg/dL; and creatinine ≤ 1.5 mg/dL. The following patients were excluded from the study: patients with a risk of vomiting for other reasons (symptomatic brain metastasis, meningeal infiltration, epilepsy, active peptic ulcer, gastrointestinal obstruction, concomitant abdominal or pelvic radiotherapy, etc.); and pregnant, nursing, or possibly pregnant women. After the protocol and informed consent form were approved by the institutional review board (IRB) at the facility, patients who gave written informed consent were enrolled. All studies were conducted in accordance with the principles of Good Clinical Practice (GCP) and the basic principles of the Declaration of Helsinki.

Design and treatment

This was an open-label study. A total of 20 patients were randomized to receive aprepitant at an oral dose of 125/80 mg (125 mg on day 1 and 80 mg on days 2–5; $n = 10$) or 40/25 mg (40 mg on day 1 and 25 mg on days 2–5; $n = 10$). In addition, all patients received standard antiemetic therapy consisting of intravenous granisetron (40 μg/kg on day 1) and intravenous dexamethasone sodium phosphate (on days 1–3). In this study, the dose of intravenous dexamethasone was 6 mg on day 1 and 4 mg on days 2 and 3 in the 125/80-mg group and 8 mg on day 1 and 6 mg on days 2 and 3 in the 40/25 mg group. Although, in the antiemetic guidelines [4–6], it is recommended that dexamethasone is administered at a dose of 12 mg on day 1 and at a dose of 8 mg on day 2 and thereafter in combination with aprepitant 125/80 mg, the dose of dexamethasone in this study was determined in order to compare the clearance of dexamethasone in this study with that obtained from Japanese cancer patients in the absence of aprepitant at a dose of 12 mg dexamethasone on day 1 [10].

Pharmacokinetic evaluation

Blood samples for measurement of plasma aprepitant concentration were collected before administration of aprepitant on days 1–5 and 1, 2, 3, 5, 9, 11, and 24 h after administration of aprepitant on day 1 and on day 5 only. In addition, a separate set of blood samples for measurement of plasma dexamethasone concentration were collected immediately, 15 min, 30 min, and 1.5, 3.5, 7.5, 9.5, and 22.5 h after administration of dexamethasone on day 1.

Methods for measurement of plasma aprepitant and dexamethasone concentrations

For each subject, venous blood was collected in an EDTA 2Na-treated tube at each sampling time point and immediately centrifuged at approximately 1,500*g* (approximately 3,000 rpm) for 10 min at room temperature. Then, the resultant plasma was transferred to a polypropylene tube and stored frozen at −20°C. The plasma concentrations of aprepitant and dexamethasone were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS). After methanol was added to plasma, the internal standard and carbonate buffer (for aprepitant) or ammonium acetate buffer (for dexamethasone) were added and mixed. Then, *t*-butyl methyl ether (for aprepitant) or diethyl ether (for dexamethasone) was added to and mixed with the plasma sample and centrifuged. After the aqueous layer was frozen in a methanol/dry ice bath, the entire organic layer was collected in a tube and placed under

nitrogen stream at approximately 40°C to remove the solvent. The residue was suspended in ammonium acetate aqueous solution (containing formic acid)/acetonitrile (for aprepitant) or methanol/water (for dexamethasone) for use in LC/MS/MS.

The pharmacokinetic parameters of aprepitant and dexamethasone were calculated by non-compartment analysis using WinNonlin Professional® software Ver.4.0.1 (Pharsight Corporation, Mountain View, CA, USA). The maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and area under the plasma concentration–time curve from 0 to 24 h post-dose ($AUC_{0-24\ h}$) were calculated for aprepitant, and the C_{max}, area under the plasma concentration–time curve from 0 to infinity ($AUC_{0-\infty}$), $t_{1/2}$, total clearance (CL_{tot}), and volume of distribution at steady state (V_{ss}) were calculated for dexamethasone.

Assessment of substance P

Before administration of aprepitant on days 1–5, venous blood was collected in an ethylenediaminetetraacetic acid (EDTA)/aprotinin-treated tube from each subject and inverted to mix. After blood was immediately centrifuged at 1,500*g* (approximately 3,000 rpm) for 10 min at 4°C, 0.5 mL of plasma was stored frozen at –20°C. The plasma substance P concentration was measured by enzyme immunoassay (EIA).

Statistical analysis

To assess ethnic differences in the pharmacokinetics of aprepitant, the C_{max} and $AUC_{0-24\ h}$ at a dose of 125 mg in Japanese cancer patients were compared with those in non-Japanese cancer patients [12] by calculating the geometric mean ratio (Japanese/non-Japanese) and its 90% confidence interval for each parameter.

To assess the validity of adjusting the dose of dexamethasone in the 125/80 and 40/25 mg groups, the exposure levels of dexamethasone were compared. The C_{max} and $AUC_{0-\infty}$ of dexamethasone in each group were used to calculate the geometric mean ratio (125/80 mg group/40/25 mg group) and its 90% confidence interval for each parameter. In addition, the clearance of dexamethasone in each group was compared with that calculated in the absence of aprepitant in Japanese cancer patients [10].

For substance P, the plasma concentration on each measurement day was used to assess the change on day 2 and thereafter, and these changes were evaluated by paired *t* test.

This study was designed and funded by Ono pharmaceutical Co., Ltd. and Merck & Co., Inc., the manufacturer of aprepitant.

Results

Patients

A total of 20 patients (10 in the 125/80 mg group and 10 in the 40/25 mg group) were included. Patients' characteristics are shown in Table 1. There were 18, 1, and 1 patients with non–small cell lung cancer, small-cell lung cancer, and mesothelioma, respectively. All were treated with at least the highly emetogenic chemotherapeutic agent cisplatin (≥70 mg/m^2). The two groups were generally similar in age, sex, height, and body weight.

Pharmacokinetics of aprepitant

All 20 enrolled patients were included in the pharmacokinetic analysis. The pharmacokinetic parameters of aprepitant are shown in Table 2. In the 125/80 mg group, the $AUC_{0-24\ h}$ on days 1 and 5 increased out of proportion to the dose, compared with that in the 40/25 mg group.

The geometric mean ratio and its 90% confidence interval (CI) of the C_{max} and $AUC_{0-24\ h}$ of aprepitant in Japanese cancer patients to non-Japanese cancer patients was 1.09 (0.79–1.52) and 1.12 (0.87–1.45), respectively,

Table 1 Characteristics of patients

Characteristics	125/80 mg regimen $n = 10$	40/25 mg regimen $n = 10$
Male/female (*N*)	6/4	7/3
Age (years)		
Mean (S.D.)	59.7 (6.7)	63.6 (5.9)
Range	47–71	55–72
Height (cm)		
Mean (S.D.)	161.16 (9.91)	161.24 (12.97)
Range	147.0–179.5	139.2–177.3
Weight (kg)		
Mean (S.D.)	55.72 (10.28)	56.86 (14.17)
Range	42.2–76.6	42.4–82.7
Primary cancer diagnosis (*N*)		
Non–small cell lung cancer	9	9
Small-cell lung cancer	1	0
Mesothelioma	0	1
Chemotherapy regimen (*N*)		
Cisplatin + gemcitabine	3	5
Cisplatin + tegafur/gimeracil/oteracil	2	2
Cisplatin + vinorelbine	2	2
Cisplatin + etoposide	2	0
Cisplatin + docetaxel	1	1

Table 2 Summary of the pharmacokinetics of aprepitant on days 1 and 5

Day	Parameter	125/80 mg regimen	40/25 mg regimen
1	C_{max} (ng/mL)	2,210 ± 870	536 ± 105
	T_{max} (h)	7.0 (3.0–9.0)	3.0 (2.0–9.0)
	$AUC_{0-24\ h}$ (ngh/mL)	30,000 ± 8,700	6,360 ± 1,350
5	C_{max} (ng/mL)	3,070 ± 850	453 ± 109
	T_{max} (h)	3.0 (2.0–9.0)	3.0 (2.0–3.0)
	$AUC_{0-24\ h}$ (ngh/mL)	46,000 ± 17,100	5,420 ± 1,680

Mean ± SD, T_{max} median (range)

C_{max}, maximum plasma concentration, T_{max}, time to maximum plasma concentration, $AUC_{0-24\ h}$ area under plasma concentration–time curve from 0 to 24 h post-dose

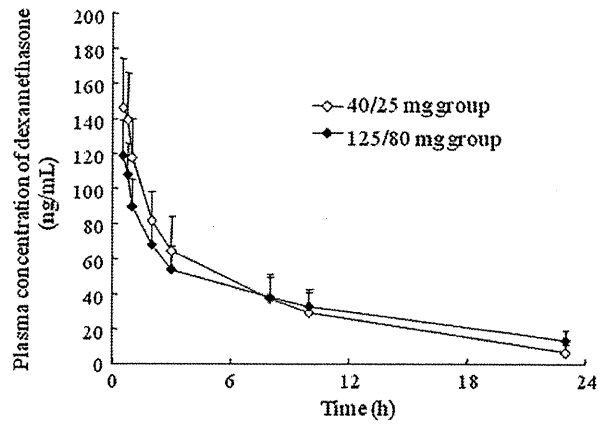

Fig. 1 Time profile of plasma dexamethasone concentration in each treatment group (day 1). Mean + SD ($n = 10$)

showing little differences between Japanese and non-Japanese groups in the pharmacokinetics of aprepitant.

Pharmacokinetics of dexamethasone

For dexamethasone, the pharmacokinetic parameters and time profile of plasma concentration on day 1 in the 125/80 and 40/25 mg groups are shown in Table 3 and Fig. 1, respectively. The geometric mean ratio (90% CI) of C_{max} and $AUC_{0-\infty}$ of dexamethasone on day 1 in the 125/80 mg group to the 40/25 mg group was 0.83 (0.73–0.94) and 1.15 (0.88–1.50), respectively, showing that although the C_{max} tended to be high in the 40/25 mg group, the $AUC_{0-\infty}$was similar between the two treatment groups. To verify the dose reduction of dexamethasone in cancer patients who receive emetogenic cancer chemotherapy in combination with aprepitant, we compared the clearances of dexamethasone in this study with that obtained from Japanese cancer patients in the absence of aprepitant at a dose of 12 mg on day 1 (13.3 L/h) [10]. In the 125/80 and 40/25 mg groups (dexamethasone at a dose of 6 and 8 mg on day 1, respectively), the clearance of dexamethasone was 6.48 and 10.0 L/h, respectively. That is, the clearances of dexamethasone in the 125/80 and 40/25 mg groups decrease by approximately 52 and 25%, respectively. These results demonstrate the validity of reducing the dose of dexamethasone by 50 and 25% in the 125/80 and 40/25 mg groups, compared with the dose of dexamethasone in the absence of aprepitant.

Table 3 Pharmacokinetic parameters of dexamethasone in each treatment group (on day 1)

Parameter	125/80 mg regimen (Dexamethasone 6 mg)	40/25 mg regimen (Dexamethasone 8 mg)
C_{max} (ng/mL)	121 ± 17	147 ± 27
AUC_{0-t} (ngh/mL)	823 ± 213	838 ± 253
$AUC_{0-\infty}$ (ngh/mL)	1,020 ± 300	899 ± 287
$t_{1/2}$ (h)	9.6 ± 2.4	5.7 ± 1.4
CL_{tot} (L/h)	6.48 ± 2.50	10.0 ± 4.1
V_{ss} (L)	74.6 ± 14.3	65.5 ± 11.7

Mean ± SD

C_{max} maximum plasma concentration, AUC_{0-t}, area under plasma concentration–time curve from 0 to the last measurable concentration, $AUC_{0-\infty}$, area under plasma concentration–time curve from 0 to infinity, $t_{1/2}$ elimination half-life, CL_{tot} total clearance, V_{ss} volume of distribution at steady state

Evaluation of plasma substance P

The time profile of plasma substance P concentration after administration of chemotherapeutic agents in all 20 patients (days 1–5) is shown in Fig. 2. The substance P

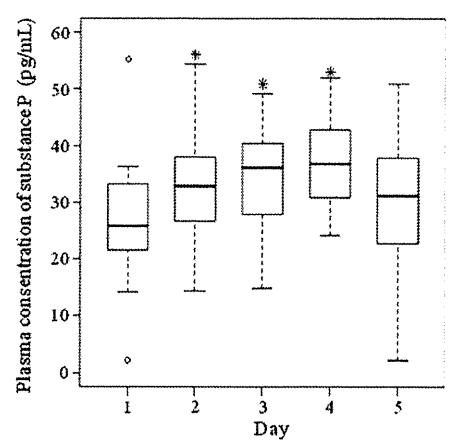

Fig. 2 Time profile of plasma substance P concentration ($n = 20$). *Top bar* highest value in the range of quartile × 1.5; *lower bar* lowest value in the range of quartile × 1.5; *top of box* upper quartile; *bottom of box* lower quartile; middle bar: median value; *circles* outliers $^*P < 0.05$ compared with baseline (day 1) concentration

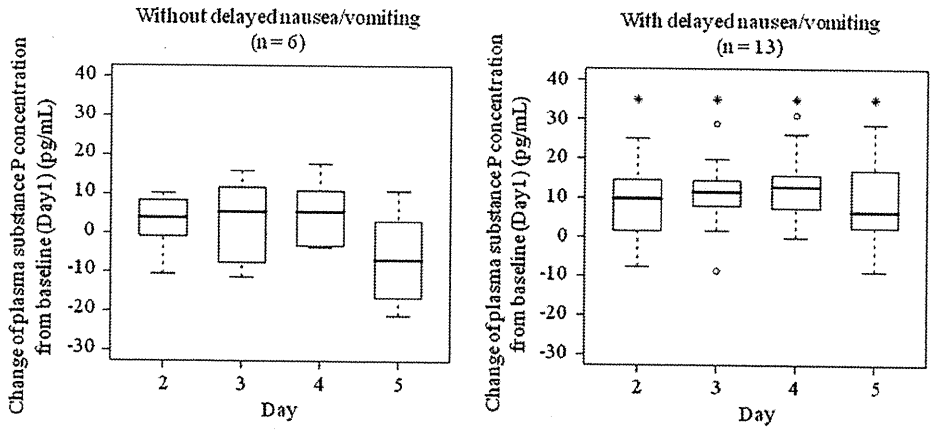

Fig. 3 Change in plasma substance P concentration ($n = 19$). *Top bar* highest value in the range of quartile × 1.5; *lower bar* lowest value in the range of quartile × 1.5; *top of box* upper quartile; *bottom of box* lower quartile; *middle bar* median value; *circles* outliers $*P < 0.05$ between days 2 and 5 compared with baseline (day 1)

concentration significantly increased on days 2–4, compared with that on day 1 (baseline) ($P < 0.05$, paired t test).

There was no difference in the change in the plasma substance P concentration between the 125/80 and 40/25 mg groups (data not shown). The change in substance P concentration in plasma from baseline (the concentration before the start of treatment with aprepitant) in patients with or without delayed nausea/vomiting is shown in Fig. 3. One patient had missing data for the substance P concentration on day 1, and so we analyzed the change in substance P concentration from baseline (day 1) in 19 patients. In patients with delayed nausea/vomiting, substance P concentration increased significantly between days 2 and 5 compared with baseline (day 1) ($P < 0.05$, paired t test). On the other hand, in patients without delayed nausea/vomiting, the increase in substance P concentration on days 2–5 was not statistically significant.

Discussion

In this study, the pharmacokinetics of aprepitant and dexamethasone were determined in Japanese cancer patients receiving emetogenic chemotherapeutic agents. There were no differences in the pharmacokinetics of aprepitant between Japanese and non-Japanese cancer patients. In addition, we showed the validity of dose adjustment of dexamethasone used in combination with aprepitant (i.e., reducing the dose of dexamethasone by 50% when combined with 125 mg of aprepitant). We also found that the blood concentration of substance P, which is deeply involved in the pharmacological effects of aprepitant, increased after administration of chemotherapeutic agents.

In the present study, the geometric mean ratio of the C_{max} and $AUC_{0-24\ h}$ in Japanese cancer patients to non-Japanese cancer patients was 1.09 and 1.12, respectively, indicating no ethnic differences in the pharmacokinetics of aprepitant. In the aprepitant 125/80 mg group, more than dose-proportional increase in $AUC_{0-24\ h}$ occurred on both days 1 and 5, compared with that in the 40/25 mg group. Aprepitant is primarily metabolized by CYP3A4 [13], and this more than proportional increase in the $AUC_{0-24\ h}$ of aprepitant may reflect saturated metabolism of aprepitant via CYP3A4 as previously reported in healthy non-Japanese volunteers [14].

In this study, granisetron hydrochloride and dexamethasone sodium phosphate were concomitantly used as standard antiemetic therapy. Aprepitant–dexamethasone interaction causes the increase in plasma dexamethasone concentration [9], and it has been suggested that this drug interaction may also cause a slight increase in the incidence of infection-related serious adverse events [15]. Since the AUC of dexamethasone (p.o.) has been shown to increase approximately two times after administration of aprepitant at a dose of 125 mg on day 1 in healthy adults [9], the dose of dexamethasone has to be reduced by 50% when used in combination with 125 mg of aprepitant. While oral dexamethasone was used in the report by McCrea et al. [9], this was the first full pharmacokinetic study of intravenous administration of dexamethasone when used in combination with aprepitant in cancer patients actually receiving chemotherapeutic agents. In the 125/80 mg group, the clearance of intravenous dexamethasone decreased by approximately 52% from that calculated in the absence of aprepitant, justifying a 50% dose reduction of intravenous dexamethasone used in combination with 125 mg of aprepitant in cancer patients as McCrea et al. demonstrated in healthy adults [9]. And the results from this full pharmacokinetic study also supported a report using a population pharmacokinetics model by Nakade et al. [10] that the clearance of intravenous dexamethasone used in combination with aprepitant at a dose of 125 mg decreased by 47.5% of that in the absence of aprepitant.

While aprepitant may exert its antiemetic effect during chemotherapy, by inhibiting the binding of substance P to

the NK_1 receptor in the vomiting center [1], few studies have been conducted to investigate the relationship between the blood pharmacokinetics of substance P and nausea/vomiting during treatment with chemotherapeutic agents in humans. Substance P has been shown to be co-localized with serotonin in enterochromaffin cells in the gastrointestinal tract [16] and cross the blood–brain barrier in animals [17]. These reports raise the possibility that substance P of peripheral origin may act centrally to induce emesis. However, it is still not shown whether exocytotic release of substance P from enterochromaffin cells in the gastrointestinal tract occurs after administration of emetogenic agents. This study showed that the plasma substance P concentration significantly increased on days 2–4 after administration of chemotherapeutic agents. It was also shown that the plasma substance P concentration significantly increased only in patients with delayed nausea/vomiting. These results, as well as the report from Higa [18], support the possibility that the elevation of the plasma substance P concentration by emetogenic chemotherapeutic agents may be involved in the pathogenesis of CINV, especially in the delayed phase. The plasma substance P concentration ranged from 0 to 1,608 pg/mL in a report by Higa et al. [18] and from 2–55 pg/mL in the present study. The cause of this difference is unknown, but may be attributed to different assay kits used to measure the substance P concentration (Higa et al. used R&D systems, and we used Cayman Chemical).

In conclusion, this study demonstrated similar plasma pharmacokinetics of aprepitant in Japanese and non-Japanese, the validity of reducing dexamethasone dose, and the existence of increased substance P concentration in patients receiving highly emetogenic cancer chemotherapy. Further studies are required to clarify whether measurement of the plasma pharmacokinetics of substance P may be a clinically meaningful marker for CINV in patients receiving emetogenic agents.

Conflict of interest None.

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ORIGINAL PAPER

Prognosis of small-cell lung cancer since the introduction of amrubicin

Hidekazu Suzuki · Tomonori Hirashima · Masashi Kobayashi · Shinji Sasada · Norio Okamoto · Motohiro Tamiya · Yuka Matsuura · Naoko Morishita · Nobuko Uehara · Kaoru Matsui · Ichiro Kawase

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Abstract Several studies have demonstrated the effectiveness of amrubicin (AMR) in small-cell lung cancer (SCLC). This study aimed to assess the change in the prognosis of SCLC before and after the commercial availability of AMR. We retrospectively analyzed data from 243 patients with newly diagnosed SCLC. Patients diagnosed before the start of the sale of AMR (January 1997–May 2002) constituted Group A, and patients diagnosed after its introduction (December 2002–December 2006), constituted Group B. The overall survival and demographic factors of the 2 groups were compared. Similar comparisons were also performed on subsets. Median survival time (MST) was 313 days for Group A and 388 days for Group B ($P = 0.031$). Group B with limited disease (LD) demonstrated a significantly longer median survival time (321 vs. 506 days; $P = 0.022$) than Group A, whereas no significant difference was noted between the groups of patients with extensive disease (ED) (296 vs. 280 days; $P = 0.895$). In the subset of refractory relapse of LD, the MST was clearly longer in Group B than in Group A (220 vs. 321 days; $P < 0.001$). Multivariate analysis for LD patients indicated that performance status (hazard ratio 2.072; $P = 0.003$) and commercial availability of AMR (0.596; $P = 0.022$) are significant factors. The present study has demonstrated prolonged survival times for LD patients since the start of the sale of AMR. The use of AMR in ED patients requires further investigations.

Keywords Amrubicin · Limited disease · Prognosis · Refractory relapse · Retrospective study · Small-cell lung cancer

Introduction

Lung cancer ranks high among the causes of cancer death in developed countries. Small-cell lung cancer (SCLC) accounts for approximately 13% of all lung cancers [1], and 5-year survival rates of SCLC remain low. The first-line therapy is cisplatin (CDDP) + etoposide (ETP) + concurrent radiotherapy in the case of the limited disease (LD) type of SCLC [2]; CDDP + ETP or CDDP + irinotecan (CPT) in the case of the extensive disease (ED) type of SCLC [3]. This disease recurs in the vast majority of patients.

Many agents have been tried in second-line treatments, although results have shown limited effectiveness. At present, topotecan (TOP) is widely used as a second-line chemotherapy in European and North American countries. However, TOP as second-line chemotherapy is not satisfactory, as it resulted in a response rate of 7% and an MST of 25.9 weeks [4]. The response rate was 26% in a Japanese phase II study in which TOP was used for patients with recurrent SCLC [5].

As a new agent for SCLC, amrubicin (AMR) became commercially available in Japan in December 2002, earlier than in the rest of the world. AMR is an anthracycline derivative and seems to exert its anti-tumor effect primarily by acting on DNA topoisomerase II to stabilize a cleavable complex [6].

H. Suzuki (✉) · T. Hirashima · M. Kobayashi · S. Sasada · N. Okamoto · M. Tamiya · Y. Matsuura · N. Morishita · N. Uehara · K. Matsui · I. Kawase
Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 3-7-1 Habikino Habikino-shi, Osaka 583-8588, Japan
e-mail: suzukih@opho.jp

The effectiveness of AMR in SCLC has been established. Onoda et al. conducted a phase II study of single-agent AMR as second-line therapy and reported that the response rate was 50% for patients with refractory relapse and 52% for those with sensitive relapse [7]. In addition, Inoue et al. performed a randomized phase II study to compare TOP with AMR as second-line therapy, and reported that in 60 patients included in the study, the response rate was 38 versus 13%, and the median progression-free survival (PFS) was 3.5 versus 2.2 months [8].

In Japan, at present, AMR is widely used in practice, and several years have passed since the start of its sale. It is expected that the commercial availability and increasing popularity of this promising agent as a second-line therapy will contribute to the improvement of overall survival in patients with SCLC, although this has not yet been confirmed yet. Under these circumstances, we performed a retrospective analysis to compare survival between before and after AMR sale and to identify factors that influence AMR-related changes in overall survival in patients with SCLC.

Patients and methods

Patient selection

Two hundred and eighty-three patients who were newly diagnosed with SCLC at our hospital between January 1997 and December 2006 and who received a first-line therapy were retrospectively analyzed on the basis of their medical records. Patients diagnosed and treated between January 1997 and May 2002 were assigned to the pre-AMR sale group (Group A), and those who were treated and diagnosed between December 2002 and the end of December 2006 formed the post-AMR sale group (Group B). Patients with PS 4 were excluded from the analysis, as were those diagnosed and treated within 6 months prior to the start of the AMR sale (i.e., between June and November 2002), since these patients were considered to fall into the category of patients in a transient period. Patients who underwent radical surgery were also excluded.

LD was defined as a tumor confined to one-hemithorax, including bilateral mediastinal lymphnodes, and supraclavicular lymph nodes. Any involvement beyond that mentioned above was defined as ED. Information on survival was, as a rule, calculated from the date of initiation of treatment with an anti-cancer agent. When the starting date of treatment was unknown, survival time was calculated from the date of diagnosis. The survival time represented the number of days from either starting point to death. Those patients who were lost due to change of hospital or those who survived until the end of the follow-up period were regarded as censored cases. The maximum follow-up period was set at 3 years.

Therapy and relapse type

A 3-day consecutive administration of AMR represented 1 cycle; these cycles were repeated every 3 weeks from the starting date. Those patients for whom information available for efficacy evaluation was insufficient or those for whom treatment was withdrawn because of adverse reactions were regarded as "not evaluable" cases. As a rule, the anti-tumor effect was based on the Response Evaluation Criteria In Solid Tumors (RECIST). For relapse typing, refractory relapse was defined as failure to achieve partial remission (PR) or greater response to first-line therapy, or relapse within 90 days after the last administration of anti-cancer therapy. Sensitive relapse was defined as relapse $\geq$90 days after first-line therapy and the last administration of anti-cancer therapy. For chest irradiation therapy, implementation of radical irradiation was defined as "irradiation performed", regardless of whether it was carried out consecutively or simultaneously. In addition, we investigated whether prophylactic cranial irradiation (PCI) was performed. When any change was made to a first-line treatment, including treatment discontinuation because of an adverse reaction, the post-change regimen was defined as second-line regimen. For the category of sensitive relapse, repeated administration of the same regimen was also defined as second-line therapy.

Statistical analysis

Statistical analysis was performed using software R (version 2.10.0) [9]. Kaplan–Meier survival analysis was performed, and log-rank tests were applied. Multivariate analysis using the Cox proportional hazard model was performed on the survival time data, for which gender, age, PS, as well as pre- and post-AMR sale were used as variables. Demographic factors were statistically analyzed using the chi-square test.

Results

On screening medical records, it was revealed that 283 patients started to receive chemotherapy at our hospital during the specified period. Of these, 243 patients, consisting of 134 in the pre-AMR sale group i.e., those diagnosed and treated between January 1997 and June 2002 (Group A), and 109 in the post-sale group i.e., those diagnosed between December 2002 and December 2006 (Group B), were included in the analysis. Eleven patients with PS 4, 21 patients who were diagnosed and treated in

the transient period, and 8 patients who underwent radical surgery were excluded from the analysis. Table 1 shows the demographic factors. No significant differences were noted between the 2 groups in age, gender, disease stage, or PS. For LD patients (Table 2), the 2 groups did not significantly differ in the proportion of patients who presented with sensitive relapse, those who experienced refractory relapse, or those who underwent radical radiotherapy or PCI, whereas a significant difference was found in the rate of implementation of second-line therapy. For ED patients, the number of women was significantly smaller in Group B (Table 3).

Figure 1 shows the overall survival curves. As for overall survival, the MST was 313 days (95% confidence interval (CI): 257–348 days) for Group A and 388 days (95% CI: 324–486 days) for Group B, showing a significant prolongation in Group B ($P = 0.031$). Evaluation by disease stage revealed that for the survival curves of LD patients (Fig. 2a), the MST was 321 days (95% CI: 248–456 days) for Group A and 506 days (95% CI: 472–1087 days) for Group B, indicating a significant improvement in Group B ($P = 0.022$). The survival curves of ED patients (Fig. 2b) indicated that the MST was 296 days (95% CI: 241–348 days) for Group A and 280 days (95% CI: 262–367 days) for Group B, showing no significant difference ($P = 0.895$).

Comparison of the 2 groups by relapse type for LD patients revealed that for the survival curves of patients with refractory relapse (Fig. 3a), the MST was 220 days (95% CI: 184–276 days) for Group A and 321 days (95% CI: 282–503) for Group B, showing a significant improvement in Group B ($P < 0.001$). The survival curves of those patients with sensitive relapse (Fig. 3b) indicated an MST of 528 days (95% CI: 434–INF) for Group A and of 894 days (95% CI: 498—INF) for Group B ($P = 0.325$).

Table 1 Baseline characteristics of all patients

	Group A	Group B	*P*-value
No. of patients	134	109	
Median age	69	68	0.600
(Range)	(42–87)	(44–81)	
Gender			
Male	113	98	0.278
Female	21	11	
PS			
0,1	84	75	0.834
2,3	42	34	
Stage			
LD	64	58	0.474
ED	70	51	

Group A, January, 1997–May, 2002; Group B, December, 2002–December, 2006; *N* number, *PS* performance status, *LD* limited disease, *ED* extensive disease

Table 2 Therapy-related background of limited disease (LD) patients

	Group A	Group B	*P*-value
N of patients	64	58	
Median age	69	69	0.600
(Range)	(42–87)	(44–81)	
Gender			
Male	53	49	0.803
Female	11	9	
PS			
0,1	51	41	0.249
2,3	13	17	
PCI	8	15	0.184
Thoracic RT	27	31	0.561
Response rate	78.1%	89.7%	0.705
Relapse type			
Sensitive	22	27	0.849
Refractory	32	25	0.765
Unknown	3	0	
No relapse	7	6	
Second-line Cx	21	44	0.013
CPT	12	28	0.001
AMR	2	28	<0.001

Group A January, 1997–May, 2002, *Group B* December, 2002–December, 2006, *N* number, *PS* performance status, *PCI* prophylactic cranial irradiation, *RT* radiation therapy, *Cx* chemotherapy, *CPT* irinotecan, *AMR* amrubicin

Multivariate analysis

For LD patients, multivariate analysis using the Cox proportional hazard model was performed (Table 4), using the following variables: age (above and below 70 years), PS, gender, AMR sale, and whether PCI was implemented. The resulting hazard ratio was 2.072 (95% CI: 1.278–3.357) for PS ($P = 0.003$) and 0.596 (95% CI: 0.384–0.929) for AMR sale ($P = 0.0220$), indicating that these 2 variables are significant factors. Age, gender, and PCI were not significant factors for overall survival.

Discussion

Our study demonstrated an improvement in the overall survival time of patients with SCLC after the commercial availability of AMR. The analysis by disease stage revealed that this effect of prolonging the survival time was observed for LD patients, whereas the survival of ED patients was not prolonged. In particular, it is noteworthy

Table 3 Therapy-related background of extensive disease (ED) patients

	Group A	Group B	*P*-value
N of patients	70	51	
Median age	69	67	0.913
(Range)	(42–83)	(48–81)	
Gender			
Male	60	49	<0.001
Female	10	2	
PS			
0,1	41	34	0.365
2,3	29	17	
Response rate	77.1%	74.5%	0.987
Relapse type			
Sensitive	16	11	0.935
Refractory	50	39	0.912
Unknown	4	0	
No relapse	0	1	
Second-line Cx	25	41	<0.001
CPT	18	32	<0.001
AMR	6	29	<0.001

Group A January, 1997–May, 2002, *Group B* December, 2002–December, 2006, *N* number, *PS* performance status, *Cx* chemotherapy, *CPT* irinotecan, *AMR* amrubicin

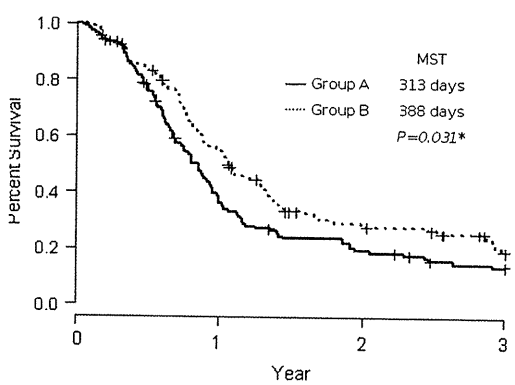

Fig. 1 Overall survival curves. Group A (*solid line*) represents the patients before the commercial availability of AMR and Group B (*broken line*) after the marketing of AMR. *AMR* amrubicin hydrochloride, *MST* median survival time

that the survival time was longer in patients with refractory relapse, who have been highly resistant to therapy. This finding achieved with AMR might have substantially contributed to the improvement in overall survival.

Patients with sensitive relapse typically respond well to chemotherapy, and second-line therapy achieves high response rates. For example, even TOP resulted in a response rate of 24.3% when administered as second-line therapy to patients with sensitive relapse [10]. As such, these patients seem to easily benefit from anti-cancer agents. In our present study, if the prolonged survival time in patients with sensitive relapse had been related to the prolongation of overall survival of recurrent SCLC, it might have merely resulted from continuing administration of anti-cancer therapy. In the present study, however, we could not make a decisive judgment on how effective AMR is in LD patients with sensitive relapse. On the other hand, we found that the survival time of LD patients with refractory relapse was prolonged, which then contributed to prolongation of the overall survival of patients with recurrent SCLC, and this finding seems to be highly important. In other words, for LD patients with sensitive relapse, any type of selected drug contributes to prolongation of the survival time in its own way. For LD patients with refractory relapse, AMR is expected to be effective as single-agent second-line therapy.

A limitation of the present study is that there might be other possible reasons for the prolonged prognosis, e.g., a possible influence of PCI, positive implementation of a second-line therapy in which CPT was used as a key agent, and other unknown reasons. For the LD patients with sensitive relapse included in our analysis, no conclusive decision can be made at present because the follow-up period was too short, and the number of patients was too few. For PCI, a meta-analysis of LD patients who attained complete response (CR) and underwent PCI revealed improvement of the 3-year survival rate by 5.4% [11]. Even ED patients who underwent PCI presented significantly longer survival times [12]. Among the subsets of LD patients in our present study, the number of patients who underwent PCI tended to be greater in Group B, and the contribution of PCI to the prolonged survival time was therefore assumed. However, this finding is inconclusive. The effects of stage migration by PET/CT and progress of the palliative care are thought as other factors. Furthermore, the reason why the median survival time for Group A was less than other reports might be related to low response rate, the progression of radiation technique and the aggressive re-treatment. Database in the US has revealed that the percentage of patients with SCLC has gradually decreased and that the overall survival time of patients with SCLC has been longer in recent years, although only slightly [1]. For example, the 5-year survival rate for LD patients was 4.9% in 1973, compared to 10% in 1998. This increase may be explained by the reduced smoking rates and the increased proportion of women among LD patients. In the present study, no significant differences were noted between Groups A and B in the ratio of men to women or the proportion of LD patients, although other possible causes besides administration of AMR may exist.

For the ED patients included in our analysis, in spite of the fact that more than half of them were treated with AMR, after its commercial availability, prolongation of

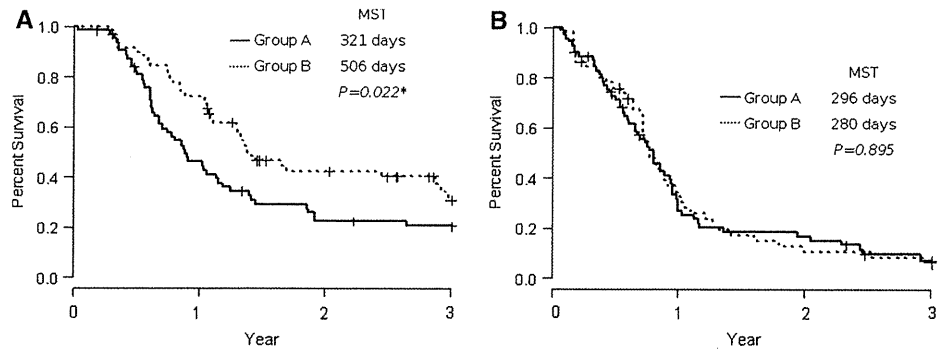

Fig. 2 **a** Survival curves for patients with limited disease (LD). **b** Survival curves for patients with extensive disease (ED). *MST* median survival time

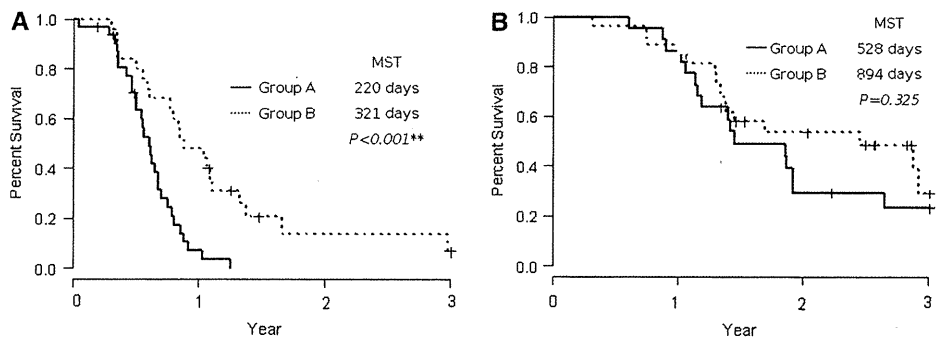

Fig. 3 **a** Survival curves for LD patients with refractory relapse. **b** Survival curves for LD patients with sensitive relapse. *MST* median survival time

Table 4 Cox proportional hazard model analysis for limited disease patients

Factor	Hazard ratio	95% CI	*P* value
Gender	1.428	(0.783–2.605)	0.250
PS	2.072	(1.278–3.357)	0.003
Age	1.240	(0.799–1.924)	0.340
AMR sale	0.596	(0.384–0.927)	0.022
PCI	0.602	(0.322–1.125)	0.110

CI confidential interval, *PS* performance status, *AMR* amrubicin, *PCI* prophylactic cranial irradiation

Table 5 (A) Amrubicin (AMR) administration by performance status (PS). (B) AMR administration timing in all therapeutic courses

	AMR	Yes	No
(A)			
PS 0,1		30	45
PS 2,3		22	12
			$P = 0.029$
Course			N of patients
(B)			
First			5
Second			34
Third			22
Fourth ~			4

AMR amrubicin, *PS* performance status, *N* number

survival was not observed. When all patients included in the present analysis were evaluated, the frequency of AMR administration was significantly lower in the subset of patients whose PS was poorer upon initial therapy (Table 5a). The reason for the observed improvements in LD patients was because their PS was maintained in second-line therapy and even third-line therapy, and therefore AMR was able to exert its effect. On the other hand, the PS of ED patients worsen frequently on relapse. In addition, their organ functions, including the hemopoietic function, tend to impair. For these reasons, it is considered that AMR was not able to exert its effect in ED patients. AMR should be positively used at relatively early time points when the bone marrow function is preserved. In our present study, AMR was administered as second- or third-line therapy in the vast majority of patients (Table 5b). In the future, an optimal timing for introduction of AMR so as to contribute to prolongation of survival in ED patients needs to be investigated. Candidate strategies may include administration of AMR to ED patients with maintained PS, that is, AMR should be used in a first- or second-line therapy, or in maintenance therapies for which an appropriate dosage needs to be determined.

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CLINICAL INVESTIGATION **Lung**

THE IMPACT OF RADIATION DOSE AND FRACTIONATION ON OUTCOMES FOR LIMITED-STAGE SMALL-CELL LUNG CANCER

NATSUO TOMITA, M.D.,* TAKESHI KODAIRA, M.D.,* TOYOAKI HIDA, M.D.,†
HIROYUKI TACHIBANA, M.D.,* TATSUYA NAKAMURA, M.D.,* RIE NAKAHARA, M.D.,*
AND HARUO INOKUCHI, M.D.*

Departments of *Radiation Oncology and †Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Purpose: To review the treatment outcomes of limited-stage small-cell lung cancer (LS-SCLC) patients and to compare the outcomes among three groups in which the total radiation doses were 45 Gy with accelerated hyperfractionation (AHF), <54 Gy with standard fractionation (SF), and ≥54 Gy with SF.

Methods and Materials: LS-SCLC patients that had been treated with chemoradiotherapy between 1997 and 2007 at Aichi Cancer Center Hospital were reviewed in this study. Of the 127 eligible patients, there were 37 patients in the AHF group, 29 in the SF <54 Gy group, and 61 in the SF ≥54 Gy group.

Results: Fifty-five patients (43%) were alive at the time of this analysis, and the median follow-up time of the surviving patients was 33 months. The median survival times were 30.0 months (95% confidence interval [CI] 16.3–43.7) for the AHF group, 14.0 months (CI 6.6–21.4) for the SF <54 Gy group, and 41.0 months (CI 33.9–48.1) for the SF ≥ 54 Gy group. As for the local control rates, and the overall and progression-free survival rates, all outcomes were significantly lower in the SF <54 Gy group than in the other two groups, although no significant difference was found between the AHF and SF ≥54 Gy groups.

Conclusions: These results suggest the importance of a high dose of radiation when using once-daily regimen. This study will support future prospective studies to establish optimal radiation doses and fractionation. © 2010 Elsevier Inc.

Small-cell lung cancer, Radiation therapy, Radiation dose, Fractionation, Accelerated hyperfractionation.

INTRODUCTION

Chemoradiotherapy is currently the standard treatment for limited-stage small-cell lung cancer (LS-SCLC) (1). Although thoracic radiotherapy (TRT) has been established as an integral component of the treatment platform for LS-SCLC, some questions regarding the optimal radiotherapy approach have also arisen. With regard to fractionation, Turrisi *et al.* determined that accelerated hyperfractionation (AHF) is superior to standard fractionation (SF) in an Intergroup Phase III study (2). However, despite the significant improvement in long-term survival, a pattern of care study found that only 10% of patients with LS-SCLC received a twice-daily regimen because of the inconvenience of twice-daily treatment sessions and the increased rate of severe esophageal toxicity seen with this regimen, whereas more than 80% received once-daily TRT (3). Although traditionally modest doses of TRT (45–50 Gy) are often used in once-daily 1.8- to 2-Gy fractions (4, 5), the optimal total dose for a once-daily regimen has not been proven. In addition, it is also still unclear whether twice-daily TRT of 45 Gy in 3 weeks is superior to a higher total dose than traditional modest doses delivered with a once-daily regimen. In this study, we reviewed the treatment outcomes of LS-SCLC patients that were treated with chemoradiotherapy at Aichi Cancer Center Hospital and compared the outcomes among three groups in which the total radiation doses were 45 Gy with a twice-daily regimen, less than 54 Gy with a once-daily regimen, and equal or greater than 54 Gy with a once-daily regimen.

METHODS AND MATERIALS

Patient selection

LS-SCLC patients that had been treated with chemoradiotherapy between 1997 and 2007 at Aichi Cancer Center Hospital and who met the eligibility criteria were enrolled into this retrospective study. The diagnosis of SCLC was confirmed by histologic or cytologic findings in all cases. Limited-stage was defined as disease confined to one hemithorax with or without bilateral supraclavicular node metastasis. The eligibility criteria consisted of no previous treatment and an Eastern Cooperative Oncology Group performance status

Reprint requests to: Natsuo Tomita, M.D., Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan. Tel: (+81) 52-762-6111; Fax: (+81) 52-752-8390; E-mail: ntomita@aichi-cc.jp

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