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

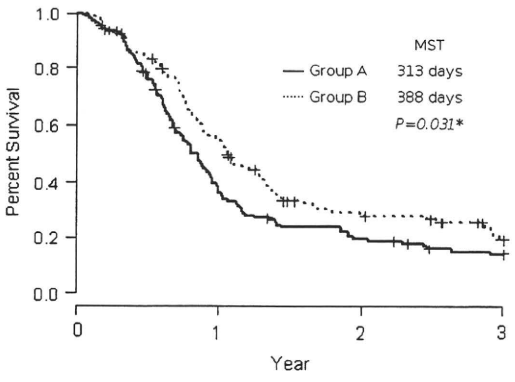

Fig. 1 Overall survival curves. Group A (*solid line*) represents the patients before the commercial availability of AMR and Group B (*broken line*) after the marketing of AMR. *AMR* amrubicin hydrochloride, *MST* median survival time

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

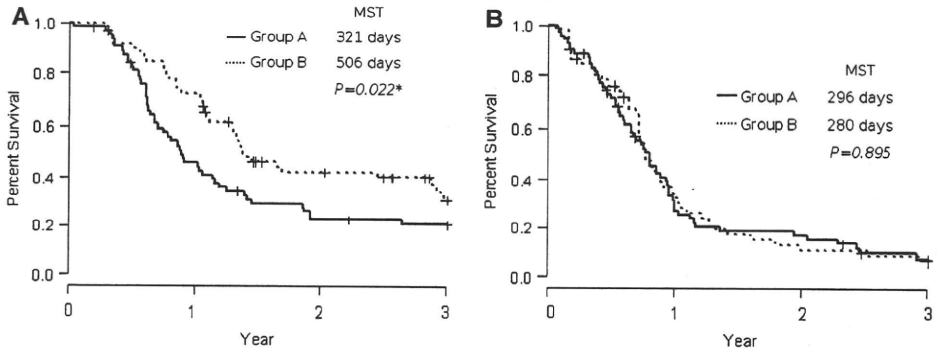

Fig. 2 **a** Survival curves for patients with limited disease (LD). **b** Survival curves for patients with extensive disease (ED). *MST* median survival time

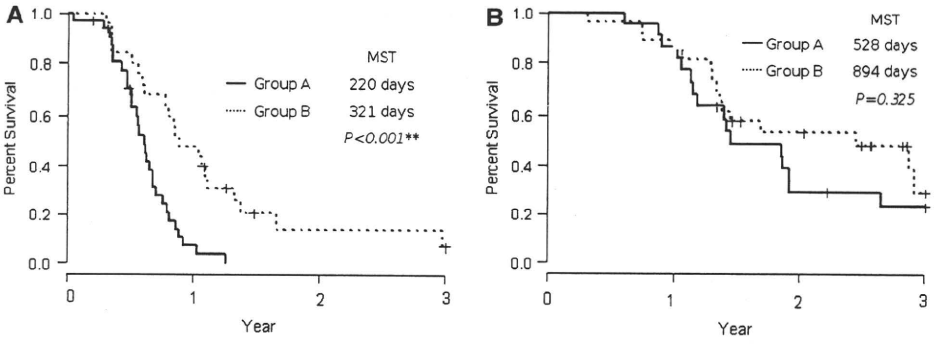

Fig. 3 **a** Survival curves for LD patients with refractory relapse. **b** Survival curves for LD patients with sensitive relapse. *MST* median survival time

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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Phase I Study of Topotecan and Cisplatin in Patients with Small Cell Lung Cancer

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Objective: A single-agent topotecan has an indication for the treatment of small cell lung cancer in Japan. Previous studies demonstrated that topotecan combined with a platinum agent could provide additional antitumor efficacy. This study was to find the recommended dose of topotecan in combination with cisplatin and preferred administration sequence in untreated patients with extensive disease small cell lung cancer for Phase II study.
Methods: Patients received topotecan as a 30 min infusion for 5 days in escalating doses (starting at 0.5 mg/m^2/day), and cisplatin at a fixed dose of 60 mg/m^2, 3 weeks cycle. This study employed the following stages: cisplatin was given before topotecan on day 1 to previously treated patients (Stage 1). After the maximum-tolerated dose level was achieved, the same schedule was applied for untreated patients (Stage 2). Subsequently, cisplatin was given after topotecan on day 5 to untreated patients (Stage 3). The recommended doses of cisplatin on day 1 and 5 schedules were estimated by considering results obtained from Stages 2 and 3, respectively.
Results: A total of 34 patients were enrolled. The maximum-tolerated doses in Stages 1–3 were estimated at 0.65, 0.65, and 1.4 mg/m^2, respectively. The recommended doses of cisplatin on day 1 and 5 schedules in untreated patients were determined at 0.65 and 1.0 mg/m^2, respectively. The major toxicity in this combination was hematological events.
Conclusions: For treatment-naive patients, the combined use of 0.65/60 mg/m^2 topotecan/cisplatin with cisplatin on day 1 schedule or 1.0/60 mg/m^2 topotecan/cisplatin with cisplatin on day 5 schedule is recommended for Phase II study.

Key words: small cell lung cancer – combination chemotherapy – topotecan – cisplatin

INTRODUCTION

Small cell lung cancer (SCLC) is often diagnosed at the extensive disease (ED) stage due to lesion location and rapid disease progression (1). Multiagent chemotherapy is the mainstay of treatment for SCLC, and combination regimens such as cisplatin + etoposide are being used as the standard therapy for ED cases (2). Topotecan, a topoisomerase-I inhibitor, has a favorable toxicity profile compared with most other agents that are active in SCLC. Topotecan has a well-characterized and predictable hematologic toxicity profile that includes neutropenia, which is manageable, short-lived and reversible. The non-hematologic effects of topotecan are generally mild and include manageable gastrointestinal toxicities (3). A single-agent topotecan showed significant activity in SCLC, particularly in patients sensitive to prior chemotherapy; therefore, the incorporation of topotecan in combination chemotherapy regimens for the future treatment of SCLC was warranted (3). Although single-agent topotecan has already an indication for the treatment of SCLC in Japan, previous preclinical and clinical studies have demonstrated that the combination of topotecan with a

platinum agent, such as cisplatin, could provide additional antitumor efficacy (4–9). In addition, one study addressed the impact of cisplatin scheduling and showed that the sequence of cisplatin before topotecan induced significantly worse hematological toxicity than the alternate sequence (10). To improve the therapeutic effect of this combination, the granulocyte colony-stimulating factor (G-CSF) was employed as concomitant therapy in our study.

Thus, we designed the present study to evaluate both administration sequences. The prime objective of the study was to determine the recommended dosage for a subsequent Phase II study from the estimation of maximum-tolerated dose (MTD) of topotecan in combination with 60 mg/m^2 cisplatin on day 1 or 5 in previously untreated patients with SCLC.

METHODS

Eligibility

Written informed consent was obtained from all patients prior to treatment. The protocol and informed consent procedures were reviewed and approved by the Institutional Review Board of each participating institute. Eligibility criteria were as follows: histologically or cytologically proven SCLC; 20–74 years old; previously treated with single-regimen chemo- and/or radiotherapy, or previously untreated patients with ED; no prior treatment with biological response modifiers within 2 weeks; adequate organic function (hemoglobin level $\geq$9.5 g/dl, leukocyte count of 4000–12 000/mm^3, neutrophil cell count $\geq$2000/mm^3, platelet count $\geq$100 000/mm^3, aspartate aminotransferase and alanine aminotransferase levels $<$2.5 times the upper limit of normal, total bilirubin value $<$1.5 mg/dl, serum creatinine below the upper limit of normal, partial pressure of arterial oxygen $\geq$60 mmHg); performance status of 0–1 on the Eastern Cooperative Oncology Group scale; a life expectancy of at least 3 months; and hospitalized patients.

Exclusion criteria included the following: serious infection or other serious concurrent disease; massive pleural effusion or ascites; interstitial pneumonia or pulmonary fibrosis; symptomatic central nervous system metastasis; concomitant malignancies; patients who received bone marrow or peripheral blood stem cell transplantation; a past history of drug allergy; actual or potential pregnancy, breast-feeding status or the intention to become pregnant in the near future; poorly controlled diabetes; previously treated with topotecan; or any other condition that was considered to make the patient ineligible for this study by the investigator.

Treatment Plan and Dose Escalation

This study employed the following three stages: Stage 1, cisplatin administration on day 1 followed by topotecan on days 1–5 to previously treated patients; Stage 2, on the same schedule as Stage 1 to previously untreated patients; and Stage 3, topotecan administration on days 1–5 followed by cisplatin on day 5 to previously untreated patients. The dose level of cisplatin was fixed at 60 mg/m^2 and the dose of topotecan was increased from 0.5 mg/m^2 followed by 0.65, 0.8, 1.0, 1.2 and 1.4 mg/m^2. The stage was moved up to the next after the MTD level was achieved, and the MTD was used as the starting dose in the next stage. Topotecan was administrated by 30 min intravenous infusion for 5 consecutive days. Cisplatin dissolved in 500–1000 ml of physiological saline was infused intravenously over 2 h either on day 1 (prior to topotecan) or day 5 (subsequent to topotecan). Immediately before and after each administration of cisplatin, hydration consisting of 1000–2000 ml of fluid infusion was given intravenously over 4 h. Treatment was repeated every 3 weeks and the next cycle could be expanded to a maximum of 35 days. At all dose levels of all stages, the prophylactic use of G-CSF was initiated from the next day of last administration of topotecan. G-CSF was administered till the recovery of leukocyte or neutrophil after nadir (recovery as either leukocyte count reached 10 000/mm^3 or neutrophil count reached 5000/mm^3).

In the present study, dose-limiting toxicity (DLT) was defined as follows: Grade 4 neutropenia lasting $\geq$4 days; Grade 3 or worse febrile neutropenia and thrombopenia ($<$20 000/mm^3); Grade 4 vasculitis, external auditory canal, fatigue, wound infection, ascites (non-malignant), constipation, central nervous system hemorrhage and hyponatremia; Grade 2 or worse middle ear/hearing, pneumonitis/pulmonary infiltrates and pulmonary fibrosis; and Grade 3 or worse other non-hematological toxicities excepting weight loss, syndrome of inappropriate antidiuretic hormone, anorexia, dyspepsia/heartburn, nausea, vomiting, incontinence and urinary frequency/urgency.

To assess the topotecan dose increase, three patients were enrolled at each dose level and the dose was increased to the next level if none of the patients displayed any DLT. If all the three patients showed DLT, then this dose level was defined as the MTD. If one of the three patients had DLT, an additional three patients were treated at the same level; if none/one of the three additional patients had DLT, the dose was increased to the next level. When two or more of the three additional patients had DLT, this dose level was defined as the MTD. If all the three additional patients showed DLT, the number of additional patients was determined by reference to results of estimation of the dose–response curve with a continual reassessment method. The recommended dose (RD) for Phase II study was determined to reflect the appearance of toxicity and antitumor effect as the drug dose less than the MTD.

Assessment of Treatment

Toxicities were assessed according to the US National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. The severity of other events not listed in the

NCI-CTC was graded as follows: Grade 1, slight; Grade 2, moderate; Grade 3, severe; and Grade 4, life threatening. During the study, complete blood cell counts and biochemistry tests were repeated at least twice weekly, whereas other investigations were repeated as needed to evaluate marker lesions. Response was evaluated according to the modified World Health Organization (WHO) criteria (11).

Table 1. Patient characteristics

	Stage 1	Stage 2	Stage 3
Cisplatin injection	On day 1	On day 1	On day 5
Prior treatment	(+)[a]	(−)	(−)
No. of patients	9	6	19
Gender			
Male	9	6	16
Female	0	0	3
Age			
Median	59	57	65
Range	23–70	50–74	48–74
Performance status (ECOG)			
0	5	1	5
1	4	5	14
Clinical stage			
I	1	0	0
III	5	0	3
IV	3	6	16

ECOG, Eastern Cooperative Oncology Group.
[a]Cases previously treated with single-regimen chemo- and/or radiotherapy.

RESULTS

Estimation of MTD

Between March 2000 and February 2005, 34 patients were enrolled in this study and all of them received chemotherapy. The characteristics of these patients are shown in Table 1 and the occurrence of DLTs is shown in Table 2.

Stage 1: Cisplatin on Day 1 and Topotecan on Days 1–5, for Previously Treated Patients

No DLT occurred at the first cycle in three patients who received a topotecan dose level of 0.5 mg/m^2, and the dose of topotecan was increased to 0.65 mg/m^2. Since one of the three patients displayed a DLT of thrombocytopenia (<20 000/mm^3), another three patients were treated at the same dose. One of the additional three patients indicated Grade 4 neutropenia lasting 4 days or more as DLTs. No more increase in dose in this stage was, however, decided by Extramural Evaluation Committee (EEC) since in three out of six cases indicated DLTs at the second cycle, although the DLTs were observed in two out of six cases in the first cycle. The MTD of this stage was estimated as 0.65 mg/m^2.

Stage 2: Cisplatin on Day 1 and Topotecan on Days 1–5, for Untreated Patients

The starting dose of topotecan in Stage 2 was 0.65 mg/m^2 based on Stage 1 results. As one of three patients showed Grade 4 neutropenia lasting 4 days or more as DLTs, additional three patients were treated at the same dose. One out of the three cases indicated thrombocytopenia (<20 000/mm^3) and Grade 4 neutropenia lasting 4 days or more as DLTs. Although two out of the six cases indicated DLTs at the first cycle, three of the six cases indicated thrombocytopenia (<20 000/mm^3) only or thrombocytopenia (<20 000/

Table 2. DLTs during the first cycle or other cycles at different dose levels

	Stage 1		Stage 2	Stage 3				
Topotecan (mg/m^2)	0.5[a]	0.65[a]	0.65[b]	0.65[b]	0.8[b]	1[b]	1.2[b]	1.4[b]
No. of assessable patients	3	6	6	4	6	3	3	3
Toxic effects with first cycle/other cycles								
Grade 4 neutropenia ≥4 days	0/0	1/0	1/0	0/0	0/0	0/0	0/0	1/0
Thrombocytopenia (<20 000/mm^3)	0/0	1/0	0/1	0/0	0/0	0/0	0/0	0/0
Grade 4 neutropenia ≥4 days and thrombocytopenia (<20 000/mm^3)	0/0	0/0	1/2	0/0	0/0	0/0	0/0	0/0
Grade3 non-hematological toxicity[c]	0/0	0/0	0/0	0/0	1/0	0/0	0/0	0/0
Gait disturbance	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/0
Atrial fibrillation	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/0

[a]Prior therapy.
[b]Therapy naive.
[c]Intravenous antibiotic injection for infection.

Table 3. Grade 3/4 toxicities in 85 cycles

	Stage 1		Stage 2	Stage 3					Overall
Topotecan (mg/m^2)	0.5	0.65	0.65	0.65	0.8	1.0	1.2	1.4	
No. of patients	3	6	6	4	6	3	3	3	34
No. of cycles	6	12	23	6	11	9	11	7	85
Mean of cycles	2	2	3.8	1.5	1.8	3	3.7	2.3	
Hematological toxicities									
Anemia	0 (0)[a]	3 (1)	4 (0)	0 (0)	0 (0)	2 (0)	1 (0)	1 (0)	32.4%
Leukopenia	1 (1)	4 (4)	6 (5)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	38.2%
Neutropenia	2 (2)	4 (4)	6 (6)	0 (0)	0 (0)	1 (1)	1 (1)	1 (1)	44.1%
Thrombocytopenia	0 (0)	3 (2)	5 (3)	0 (0)	0 (0)	1 (0)	1 (1)	1 (1)	41.2%
Non-hematological toxicities									
Nausea	0 (0)	1 (1)	3 (2)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	17.6%
Vomiting	0 (0)	1 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8.8%
Anorexia	0 (0)	1 (1)	3 (2)	0 (0)	1 (0)	0 (0)	0 (0)	1 (1)	17.6%
Interference with daily activity	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	8.8%
Infection febrile	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2.9%
Increased amylase	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2.9%

Grade by the National Cancer Institute Common Toxicity Criteria (NCI-CTC).
[a]No. of patients in the first cycle are given in parentheses.

mm^3) and Grade 4 neutropenia lasting 4 days or more after the second cycle or later. EEC decided that no more proceed at this stage. Topotecan 0.65 mg/m^2 was estimated as the MTD of Stage 2, same with Stage 1.

Stage 3: Topotecan on Days 1–5 and Cisplatin on Day 5, for Untreated Patients

The first four patients, including one case who was decided as not evaluable from infection due to retaining needle, were treated with 0.65 mg/m^2 of topotecan based on the results obtained in Stage 2, and no DLT appeared. At the next dose level of 0.8 mg/m^2, one of three patients experienced DLTs, Grade 3 of infection as intravenous antibiotic injection. Then, additional three patients were enrolled at the same dose level, and none of the additional three patients had DLT. The dose of topotecan was increased as 1.0, 1.2 and 1.4 mg/m^2 in the protocol sequence. Three patients given 1.0 mg/m^2 and three patients given 1.2 mg/m^2 tolerated their dose level without DLT. Of the three patients given 1.4 mg/m^2, one patient developed Grade 4 neutropenia lasting 4 days. Following the hematological symptom, this patient also experienced Grade 3 gait disturbance. Furthermore, one case indicated an atrial fibrillation on day 3, although the relation between atrial fibrillation and topotecan was not clearly evidenced. Dose escalation was terminated at 1.4 mg/m^2; thus, we estimated the MTD of topotecan in this stage at 1.4 mg/m^2.

Gait disturbance occurred on day 10 of the first cycle following Grade 4 neutropenia. Twenty days later, in this patient, a cerebral infarction around the right lateral ventricle was observed by head magnetic resonance imaging diagnosis. This symptom has taken the medical history of cerebral hemorrhage without aftereffect and complications of hyperlipidemia and hyperuricemia into account. Then, this adverse event was observed for recovery tendency. Atrial fibrillation in a patient, who had a history of slight supraventicular arrhythmia without concomitant medication (not conflicted to exclusion criteria), noted at 1.4 mg/m^2 topotecan dose level, appeared just after completion of topotecan administration on day 3 in the first cycle and disappeared by oral anti-arrhythmic agent on the day 4 of the first cycle.

Toxicities

All 34 patients of 85 cycles were fully assessable for toxicity. Grade 3/4 toxicities during the overall cycles are summarized in Table 3. The most common hematological toxicity was neutropenia, followed by thrombocytopenia, leukopenia and anemia. On total comparison between the first cycle and overall cycles in hematological toxicity, at 0.65 mg/m^2 of Stage 1, 0.65 mg/m^2 of Stage 2 and 1.0 mg/m^2 of Stage 3, the occurrences of anemia and thrombocytopenia were increased. Leukopenia cases in 0.65 mg/m^2 of Stage 2 and anemia cases in over 1.2 mg/m^2 of Stage 3 were also increased. Average administration cycles in each dose

Table 4. Response to treatment

	Stage 1		Stage 2	Stage 3				
Cisplatin injection (fixed at 60 mg/m^2)	On day 1		On day 1	On day 5				
Prior treatment	(+)		(−)	(−)				
Topotecan (mg/m^2)	0.5	0.65	0.65	0.65	0.8	1.0	1.2	1.4
No. of patients	3	6	6	4	6	3	3	3
CR	0	0	0	0	0	0	0	0
PR	0	2	5	1	4	2	3	2
NC	2	3	0	0	0	0	0	0
PD	1	1	1	1	1	0	0	0
NE	0	0	0	2	1	1	0	1

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable.

level in each stage were less than two cycles in 0.5 and 0.65 mg/m^2 of Stage 1 and 0.65 and 0.8 mg/m^2 of Stage 3, and over two cycles in other doses of Stages 2 and 3.

Principal non-hematological toxicities were observed in six cases of nausea and anorexia, three cases of vomiting and interference with daily activity and one case of infection febrile and increased amylase, excluded as DLT events.

Clinical Response

Clinical response is shown in Table 4. Twelve (63%) of 19 patients in Stage 3 yielded partial response (PR), whereas out of nine patients administered 1 mg/m^2 and more than 1.0 mg/m^2, seven (78%) showed PR.

Recommended Dose

The MTD of topotecan on days 1–5 for therapy-naive patients in combination with cisplatin on day 1 administration was estimated as 0.65 mg/m^2. The RD for Phase II was decided as 0.65 mg/m^2 by considering clinical response and toxicity. The MTD of topotecan in the case of cisplatin on day 5 administration was estimated as 1.4 mg/m^2. The DLTs of this dosage level were atrial fibrillation and gait disturbance in non-hematological toxicity. Since unexpected/serious non-hematological adverse events were observed at topotecan 1.4 mg/m^2 dose level, the RD was tentatively considered at 1.2 mg/m^2, in which dose level, no DLT cases were observed. However, after the first course of 1.0 mg/m^2 dose level, frequencies of Grade 3/4 anemia and thrombocytopenia, as hematological toxicities, indicated increased tendency. Thus, the RD for Phase II was decided at 1.0 mg/m^2, to secure adequate safety.

DISCUSSION

The combination of topotecan and cisplatin has been investigated in several studies. Boabang et al. (5) reported an *in vitro* study result indicating synergistic antitumor activity between topotecan and cisplatin presumably due to the inhibition of DNA repair mechanisms. Since this drug is categorized as an inhibitor against topoisomerase-I, a previous administration of a DNA-injuring drug seems to be useful (12). An *in vitro* combination effect with cisplatin to topotecan was, however, recognized either pre- or post-administration for topotecan. Compared with day 5 administration of cisplatin, day 1 administration indicated an increase in hematotoxicity from the pharmacokinetic mechanism caused by renal dysfunction suspected as subclinical renal tubular damage (10). From this consideration, a Phase I clinical study in therapy-naive SCLC patients aiming at RD finding was planned from the safety and efficacy of cisplatin day 1 and 5 administration schedules, under the G-CSF concomitant use for the prevention of leukopenia/neutropenia.

The MTD of topotecan in this study was 0.65 mg/m^2 for cisplatin day 1 administration schedule and 1.4 mg/m^2 for cisplatin day 5 administration schedule. The DLTs which lead these MTDs were hematological toxicities. At the first course, neutropenia was observed at two of six in the cisplatin day 1 administration group and one of three in the day 5 administration scheduled group. One out of six patients in the cisplatin day 1 group also experienced thrombocytopenia. As for neutropenia, the incidence was similar to the DLT in topotecan monotherapy Phase I (7,13,14). In combination therapy of cisplatin and topotecan, the DLT of thrombocytopenia was reported associated with neutropenia (7,15). In this study, toxicity data on the second and further courses were also evaluated. In this evaluation, no discrepancy was found between the first course and further courses, which established the DLT in this study as neutropenia and thrombocytopenia.

The non-hematological DLTs were gait disturbance and atrial fibrillation, which were observed in the cisplatin day 5 administration group at 1.4 mg/m^2 of topotecan. No non-hematological DLT was observed in the cisplatin day 1 administration group. Grade 3 non-hematological toxicities of nausea, vomiting, anorexia, fatigue and interference with daily activity were observed as similar to other studies such as topotecan monotherapy and cisplatin combination in which Grade 3/4 non-hematological toxicities of nausea, vomiting, anorexia, fatigue and so on were recorded (7,13,15). These DLTs seem not to be this drug specified from clinical observation on occurrence and progress. Furthermore, no occurrence of Grade 3/4 diarrhea was observed, as different from the similar drug of irinotecan (16).

The MTDs of Stages 1 and 2 were estimated by taking not only the DLTs during the first cycle but hematological toxicity after the second cycle or further cycles into account. The RD for cisplatin on day 1 schedule was estimated from

the MTD of 0.65 mg/m^2 derived from consideration on incidence increment of Grade 3/4 hematological toxicities in all cycles, although the DLT observations were seen in two of six cases in the first cycle. On the other hand, cisplatin on day 5 schedule, MTD was estimated as 1.4 mg/m^2 from the observation of DLT in two of three cases at a 1.4 mg/m^2 dose level. As for RD for Phase II, 1.2 to 1.0 mg/m^2 was recommended since hematological toxicity occurrence situations were almost equivalent between 1.2 and 1.0 mg/m^2 dose levels, then for initial dose was recommended as 1.0 mg/m^2 taking safety consideration into account, but increment to 1.2 mg/m^2 was to be allowed from the second cycle based on the occurrence situation of hematological toxicity.

Overseas, the RD for topotecan monotherapy Phase II in therapy-naive SCLC patients was 1.5 mg/m^2 (14). The RDs for cisplatin day 1 administration combination were topotecan 0.75 and cisplatin 75 mg/m^2, respectively (7,9). On the other hand, the RDs were reported as topotecan 1.50 or 1.25 mg/m^2 and cisplatin 50 mg/m^2, respectively, for therapy-naive SCLC in cisplatin day 5 administration schedule (15,17). In Japan, the RD of topotecan in monotherapy was 1.0 mg/m^2. From this study, the RD of topotecan was 65% decreased from monotherapy as 0.65 mg/m^2 in cisplatin day 1 administration schedule and there was no difference from monotherapy in cisplatin day 5 administration schedule. The topotecan RD ratio between cisplatin day 1 administration schedule and day 5 (0.65/1.0) was similar to overseas reports (0.75/1.25–1.50). Therefore, the RD of topotecan was one half of monotherapy in cisplatin day 1 administration schedule and same or 80% in cisplatin day 5 administration schedule, although cisplatin RD still remains uncertain. The reason for RD reduction in cisplatin day 1 schedule is suspected as the increment of hematotoxicity caused by topotecan clearance decrease by subclinical renal tubular damage (10).

The dose of combined cisplatin was employed at 60 mg/m^2 as same dose in the case of the similar drug of irinotecan combination (18). In this study, no DLT occurrence was observed in each three cases of topotecan 1.0 and 1.2 mg/m^2 groups and average administration course numbers were over 3, which indicated the tolerability of this combination. No significant difference in observed toxicities were found compared with monotherapy (19), and previously conducted topotecan and cisplatin combination clinical studies (7,9,15,17). These findings suggested the validity of the cisplatin dose of 60 mg/m^2 in this combination.

Since neutropenia is DLT in topotecan monotherapy (6), the prophylactic use of G-CSF was initiated on day 6 of topotecan administration in this study. As the major DLT of this study was, however, neutropenia, the administration timing of G-CSF in this study might not affect the incidence of DLT. According to Saltz et al. (19), although G-CSF administration did not affect topotecan dose increase, it was suggested that the administration of G-CSF supported prevention against secondary infection or recovery. From safety consideration, the G-CSF concomitant use in this combination seems to be practical.

In conclusion, the RDs of topotecan for 5 consecutive days in combination with 60 mg/m^2 cisplatin in a 3-week cycle were 0.65 mg/m^2 with cisplatin on day 1 with G-CSF and 1.0 mg/m^2, a maximum of 1.2 mg/m^2, with cisplatin on day 5 with G-CSF. Further Phase II study of this combination chemotherapy for advanced/metastasis SCLC as first-line therapy is ongoing.

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Conflict of interest statement

None declared.

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

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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.

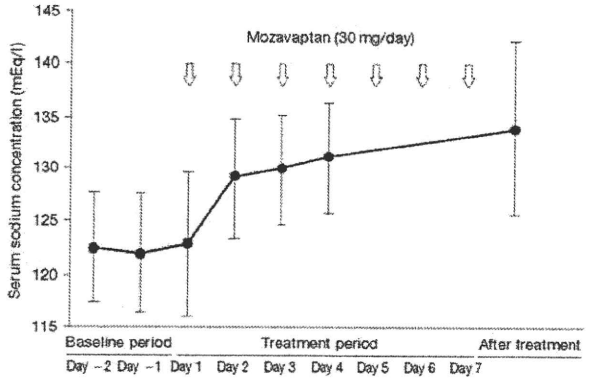

Figure 1. Time-course of serum sodium concentration (mean ± SD) in 16 cancer patients with ectopic ADH syndrome. Baseline serum sodium concentration was 122.8 ± 6.7 mEq/l. At 24 h after the first dose, serum sodium increased to 129.1 ± 5.7 mEq/l; at 24 h after completion of treatment, the value was 133.3 ± 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 $\geq$6 mEq/l increase in serum sodium concentration from baseline.

Of 12 patients who showed an increase in serum sodium concentration of $\geq$6 mEq/l from baseline at 24 h after the last dose, 7 had anorexia, nausea/vomiting, headache and/or CNS symptoms before treatment. Anorexia ($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

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Disturbance of the Growth Hormone–Insulin-like Growth Factor-1 Axis Associated with Poor Performance Status in Patients with Solid Tumors

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Objective: Hormonal imbalance characterized by excessive production of growth hormone (GH) and a low circulating concentration of insulin-like growth factor (IGF)-1 has been demonstrated in individuals with various serious conditions. However, little is known about changes in the GH–IGF-1 axis in cancer patients.
Methods: We prospectively examined the circulating levels of several hormones in 58 patients with solid tumors who were classified according to Eastern Cooperative Oncology Group performance status (PS): PS 0–1, $n = 15$; PS 2, $n = 15$; PS 3, $n = 15$; and PS 4, $n = 13$. The relations of hormone concentrations, with a focus on the GH–IGF-1 system, to PS were evaluated by Spearman's rank correlation test and regression analysis.
Results: The circulating levels of IGF-1, IGF-binding protein-3 and thyroid hormones (total T_3 and T_4) were inversely correlated with PS score. The concentration of GH was increased irrespective of PS but not statistically significant. The ratio of IGF-I to GH was inversely correlated with PS. The levels of GH and IGF-1 in all patients were also inversely correlated.
Conclusions: The present study suggests that the GH–IGF-1 axis is disturbed in patients with cancer.

Key words: growth hormone – insulin-like growth factor-1 – performance status

INTRODUCTION

Medical oncology has made substantial advances with the development of new treatment strategies based on a better understanding of cancer biology. Despite such progress, however, a large proportion of individuals with advanced cancer still experience a fatal outcome (1).

Performance status (PS) refers to the level of activity that cancer patients are capable of achieving and is an important prognostic factor independent of the anatomic extent or histological characteristics of cancer (2). After cancer diagnosis, patients will be exposed to the detrimental consequences not only of the cancer itself but also of anticancer treatment. Most patients with advanced cancer thus exhibit a deterioration in PS at some point during the course of their disease. Such a decreased PS is associated with a substantial impairment in quality of life, reduced responsiveness to anticancer therapies and increased mortality. To date, however, an effective treatment for the cancer-related deterioration in PS has not been developed, largely as a result of its multifactorial pathogenesis. New insights into the underlying pathophysiological mechanisms are likely to provide a basis for the development of effective therapeutic strategies to improve the PS of cancer patients.

Hormonal aberrations characterized by excessive production of growth hormone (GH) and a low circulating concentration of insulin-like growth factor (IGF)-1 have been

detected in patients with diverse conditions including sepsis, burns, renal failure, AIDS and anorexia nervosa as well as in individuals who have undergone surgery (3,4). Such perturbation of the GH–IGF-1 system may contribute adversely to the condition of critically ill patients, and treatments to correct the hormonal imbalance, by administration of GH or IGF-1, have been explored (4,5). Although circulating GH levels have also been found to be increased in individuals with various types of cancers, including those of the colon, lung, breast, liver and endometrium as well as lymphoma (6–12), the influence of cancer on the GH–IGF-1 axis has not been defined. We have now prospectively examined the circulating levels of several hormones in cancer patients with different PS scores and have investigated the relation of changes in hormonal profile, with a focus on the GH–IGF-1 system, to PS.

PATIENTS AND METHODS

Patients with histologically proven cancer were eligible for the study. Other inclusion criteria were an age of at least 20 years and a projected life expectancy of at least 1 month. The main exclusion criteria were blood malignancies or use of corticosteroids. The study subjects were sequentially enrolled in each institution and divided into four groups on the basis of Eastern Cooperative Oncology Group (ECOG) PS score (0–1, 2, 3 or 4), with a targeted accrual of 15 patients in each group. The number of patients enrolled in each group was counted by the patient registration office and feedback to each institution to enroll planned number of patients. Written informed consent was obtained from all patients, and the study protocol was approved by the institutional ethics committee of each of the participating institutions.

Blood samples were once collected for each patient in the early morning before the subjects had had breakfast and after they had fasted overnight or in the morning excluding 1 h after breakfast and 1 h before lunch. This was planned to avoid possible peaks of GH value in the circadian rhythm. Serum and plasma samples were obtained by centrifugation and stored at −20°C until assay. Serum GH and IGF-I levels were determined by solid-phase radioimmunoassay and immune radiometric assay, respectively. Serum triiodothyronine (total T_3), thyroxine (total T_4) and thyroid-stimulating hormone (TSH) levels were determined by electro chemiluminescent immunoassay. Serum concentrations of IGF-binding protein-3 (IGFBP-3) and thyroxine-binding globulin (TBG) were measured by competitive radioimmunoassay. All assays were performed in a blinded manner in the outside laboratory. Other laboratory variables such as total protein, albumin, cholesterol, triglyceride, C-reactive protein, creatinine and hemoglobin as well as markers of liver function were measured in routine hospital tests. Height, weight, body mass index (BMI) and food intake were also recorded for all patients. Primary endpoint of this study was defined as the relation between serum GH levels, IGF-I levels and PS.

Data are presented as means ± SD, and Spearman's rank correlation test was applied to assess the correlation between two variables. A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 58 patients (34 men and 24 women) were enrolled in the study at five centers in Japan between January 2005 and March 2006. Median age at enrollment was 64 years (range, 28–81 years). The most frequent principal diagnoses were lung cancer (33%, $n = 19$), gastric cancer (22%, $n = 13$) and colorectal cancer (19%, $n = 11$). The numbers of patients in each PS group at study entry were 15, 15, 15 and 13 for PS 0–1, 2, 3 and 4, respectively. The baseline clinical characteristics of the patients according to the PS group are shown in Table 1. Complete blood test data were available for all patients.

Food Intake, BMI and Laboratory Variables

The Spearman test revealed that PS score was inversely correlated with weight ($r = -0.54$, $P < 0.001$), BMI ($r = -0.53$, $P < 0.001$) and food intake ($r = -0.73$, $P < 0.001$) (Table 2). Inverse correlations were also apparent between PS and circulating levels of total protein ($r = -0.59$, $P < 0.001$), albumin ($r = -0.66$, $P < 0.001$), total cholesterol ($r = -0.33$, $P = 0.014$), choline esterase ($r = -0.61$, $P < 0.001$) and hemoglobin ($r = -0.37$, $P = 0.004$). PS also tended to be positively correlated with levels of alkaline phosphatase ($r = 0.23$) and lactate dehydrogenase ($r = 0.09$), but these relations did not achieve statistical significance. Significant positive correlations were detected between PS and the concentration of C-reactive protein ($r = 0.59$, $P < 0.001$) and the number of white blood cells ($r = 0.42$, $P = 0.001$).

Hormone Levels

The plasma concentration of GH was not significantly correlated with PS ($r = 0.15$, $P = 0.25$), whereas that of IGF-1 was inversely correlated with PS ($r = -0.44$, $P = 0.001$) (Table 3). An inverse correlation was also apparent between PS and the concentration of IGFBP-3 ($r = -0.39$, $P = 0.002$), the major carrier protein for IGF-1 in the circulation. The concentration of GH was inversely correlated with that of IGF-1 ($r = -0.314$, $P = 0.018$). Whereas TSH level was not correlated with PS ($r = 0.04$, $P = 0.76$), the concentrations of total T_3 (-0.57, $P < 0.001$), total T_4 (-0.38, $P = 0.003$) and TBG (-0.44, $P = 0.001$) were inversely correlated with PS. The ratio of IGF-I to GH (IGF-I/GH), a

combined indicator of GH and IGF-I, also showed correlation with PS ($r = 0.262$, $P = 0.049$) (Table 4).

Table 1. Patient characteristics

	Performance status			
	0–1	2	3	4
Assessable patients	15	15	15	13
Median age (range)	64 (49–73)	66 (50–81)	60 (28–77)	69 (54–81)
Sex (male/female)	11/4	7/8	9/6	7/6
Principal diagnosis				
Lung cancer	9	5	3	2
Gastric cancer	1	3	4	5
Colorectal cancer	2	5	4	0
Esophageal cancer	0	1	1	1
Pancreatic cancer	1	0	0	2
Breast cancer	0	0	1	1
Sarcoma	1	1	0	0
Renal cancer	1	0	0	0
Adenoid cystic cancer	0	0	1	0
Biliary tract cancer	0	0	1	0
Head and neck cancer	0	0	0	1
Cervical cancer	0	0	0	1

DISCUSSION

In this prospective evaluation of hormonal status in cancer patients, we have shown that the circulating levels of thyroid hormones (T_3 and T_4) and of components of the IGF system (IGF-1 and IGFBP-3) were inversely correlated with PS score. Given that the GH concentration also tended to be increased in patients with a high PS score, our results are indicative of an imbalance between GH and the IGF system in such patients.

Increased interpulse levels of GH have been described in critically ill patients including those with several types of cancer (4,13–15). Fasting levels of GH were also found to be significantly greater in patients with colon cancer than in control subjects (2.9 ± 3.1 versus 0.5 ± 0.2 ng/ml) (11). Our data now show a similarly high plasma concentration of GH (3.0 ± 3.7 ng/ml) in cancer patients irrespective of PS, although we did not determine values for matched controls.

Most circulating IGF-1 and IGFBP-3 are synthesized in the liver, where expression of each is increased by GH (Fig. 1). IGF-1 has a long half-life in plasma (up to 12 h), and its circulating level is highly correlated with that of GH. IGFBP-3 binds >95% of plasma IGF-1 and influences cell proliferation by controlling the access of IGF-1 to IGF receptors (16,17). In most instances, the circulating level of IGFBP-3 has been found to correlate with that of IGF-1 and is thought to reflect the status of IGF-1 in plasma. Our prospective data now show that the circulating

Table 2. Laboratory variables stratified by performance status

	Performance status				*P* value
	0–1	2	3	4	
Height (cm)	162 ± 7	158 ± 10	163 ± 9	156 ± 8	NS
Weight (kg)	58 ± 10	53 ± 15	49 ± 10	40 ± 4	<0.001
BMI (kg/m^2)	22 ± 3	21 ± 4	19 ± 4	16 ± 2	<0.001
Food intake (%)	82 ± 25	62 ± 27	27 ± 29	15 ± 19	<0.001
TP (g/dl)	7.1 ± 0.4	6.5 ± 0.4	6.2 ± 0.7	5.8 ± 0.9	<0.001
Albumin (g/dl)	3.9 ± 0.3	3.4 ± 0.5	3.0 ± 0.6	2.4 ± 0.7	<0.001
TC (mg/dl)	180 ± 32	186 ± 53	169 ± 48	125 ± 54	0.014
TG (mg/dl)	126 ± 76	113 ± 51	122 ± 80	88 ± 27	NS
ChE (IU/l)	258 ± 54	178 ± 77	174 ± 82	105 ± 48	<0.001
ALP (IU/l)	450 ± 353	480 ± 344	540 ± 446	741 ± 477	NS
LDH (IU/l)	250 ± 103	256 ± 119	323 ± 265	371 ± 434	NS
Cre (mg/dl)	0.7 ± 0.2	0.6 ± 0.2	0.9 ± 1.2	0.7 ± 0.5	NS
CRP (mg/dl)	0.8 ± 1.0	2.1 ± 2.1	4.6 ± 5.2	10.6 ± 10.5	<0.001
WBC ($10^3/\mu$l)	5.9 ± 1.9	5.3 ± 2.4	8.3 ± 4.8	11.7 ± 6.7	0.001
Hb (g/dl)	12.0 ± 1.6	10.3 ± 1.4	11.5 ± 2.4	9.3 ± 1.7	0.004
Platelets ($10^4/\mu$l)	27.9 ± 7.7	30.6 ± 22.7	25.6 ± 9.5	29.9 ± 12.6	NS

Data are means ± SD. *P* values were determined by Spearman's rank correlation test. NS, not significant; BMI, body mass index; TP, total protein; TC, total cholesterol; TG, triglyceride; ChE, choline esterase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; Cre, creatinine; CRP, C-reactive protein; WBC, white blood cells; Hb, hemoglobin.