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Improved Chemotherapy Outcomes of Patients With Small-cell Lung Cancer Treated With Combined Alkalization Therapy and Intravenous Vitamin C

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Abstract. *Background/Aim: This study aimed to investigate the effects of the combination of alkalization therapy (an alkaline diet and bicarbonate therapy) and intravenous vitamin C treatment on chemotherapy outcomes in patients with small-cell lung cancer (SCLC) (study registration: UMIN000043056). Patients and Methods: Twelve patients with SCLC in the intervention group (receiving both alkalization therapy and vitamin C treatment together with chemotherapy) were retrospectively compared to 15 patients with SCLC in the control group (receiving chemotherapy only). Results: The mean urine pH of the intervention group was significantly higher than that of the control group (7.32±0.45 vs. 6.44±0.74, respectively; p<0.005). The median overall survival for the intervention group was 44.2 months (95% confidence interval=22.0–not reached), as compared with 17.7 months for the control group (95% confidence intervaI=13.5–not reached; p<0.05). Conclusion: The combination of alkalization therapy and intravenous vitamin C treatment may be associated with favorable outcomes in patients with SCLC receiving chemotherapy.*

Small-cell lung cancer (SCLC) accounts for 10% to 15% of all lung cancer in Japan (1, 2). For nonSCLC, treatment methods, such as molecular-targeted drugs and immune checkpoint inhibitors, have recently been developed and have substantially improved treatment outcomes. On the other hand, for the treatment of SCLC, although immune checkpoint inhibitors are used, their therapeutic effects are limited, and hence the development of more effective treatment methods is urgently required.

The acidic tumor microenvironment, which is created by the highly activated glycolysis that occurs in cancer cells, is reported to be associated with cancer progression and resistance to cancer treatments (3, 4). Although in normal cells, adenosine triphosphate is usually generated *via* oxidative phosphorylation, cancer cells have unique characteristics of energy metabolism in which adenosine triphosphate is produced mainly using aerobic glycolysis (5, 6). The pH of the tumor microenvironment is regulated by acid–base transporters, such as Na^+/H^+ exchangers and monocarboxylate transporters, and protons resulting from the production of lactic acid during glycolysis are exported from cancer cells, resulting in a decrease in extracellular pH and an increase in intracellular pH (4, 7). The approach of neutralizing the acidic extracellular pH of cancer cells, such as by bicarbonate administration, has suggested more favorable outcomes of cancer treatment in several *in vivo* and *in vitro* studies (8, 9). Our group has reported some clinical studies on the effects of alkalization therapy for cancer treatment. Firstly, in patients with advanced-stage epidermal growth factor receptor mutation-positive nonSCLC, prolonged progression-free survival (19.5 months) was achieved by a regimen of low-dose epidermal growth factor receptor tyrosine kinase inhibitor (56%±22% of the standard dosage) and an alkaline diet (eating fruit and vegetables and limiting meat and milk). We also reported that an alkaline diet increased the urine pH of patients from 6.00±0.38 to 6.95±0.55 (10). Secondly, in a retrospective study of patients with advanced pancreatic cancer undergoing alkalization therapy, a prolonged median overall survival (OS) was observed in patients with a urine pH of more than 7.0 compared with those with a urine pH of 7.0 or less (16.1 *vs.* 4.7 months; $p<0.05$). Furthermore, a prolonged median OS

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for the alkalization group compared with the control group (15.4 *vs*. 10.8 months; $p<0.005$), and a significantly prolonged median OS of patients with high urine pH (pH >7.0 or ΔpH >1.0, where ΔpH was the mean urine pH before alkalization therapy subtracted from the mean urine pH after alkalization therapy) for the alkalization group compared with the control group were observed in a case–control study (11, 12).

In recent years, there have been many reports on intravenous vitamin C treatment for cancer therapy in clinical settings which have suggested that chemotherapy combined with intravenous vitamin C treatment may improve cancer treatment outcomes and reduce the toxicities of chemotherapy and radiation therapy (13-16). Regarding the mechanisms underlying the therapeutic effects of intravenous vitamin C treatment for cancer, it has been reported that dehydroascorbate (DHA), which is the oxidized form of vitamin C, inhibits glyceraldehyde 3-phosphate dehydrogenase and leads to anticancer effects. Furthermore, the suppression of inflammation by vitamin C in patients with cancer may improve cancer treatment effects (17, 18).

Based on the above, we hypothesized that the combination of alkalization therapy and intravenous vitamin C treatment may improve outcomes of patients with SCLC being treated with chemotherapy. Therefore, we conducted a retrospective study on the chemotherapy outcomes of such patients comparing the intervention group, in which patients were treated with both alkalization therapy and intravenous vitamin C with chemotherapy, with the control group, in which patients were treated with only chemotherapy.

Patients and Methods

Study design. This study was retrospectively conducted to investigate the effects of the combination of alkalization therapy and intravenous vitamin C treatment on chemotherapy outcomes in patients with SCLC. Patients with SCLC who were treated at Karasuma Wada Clinic between January 1, 2011 and December 31, 2018 were retrospectively analyzed, using medical records from Karasuma Wada Clinic. Patients were divided into two groups according to alkalization therapy and intravenous vitamin C treatment, as described below. The intervention group was defined as patients with SCLC who received both alkalization therapy and intravenous vitamin C treatment together with standard chemotherapy, and the control group was defined as patients who received chemotherapy only, with no alkalization therapy or intravenous vitamin C treatment. The rest of the patients, who received only alkalization therapy or only intravenous vitamin C treatment together with standard chemotherapy, were defined as the partial intervention group. A flowchart of the study is shown in Figure 1. All procedures were performed in accordance with the ethical principles stated in the 1995 Declaration of Helsinki. Written informed consent was obtained from each patient. This study was approved by the Institutional Review Board of the Japan-Multinational Trial Organization and was registered with UMIN Clinical Trials (UMIN000043056).

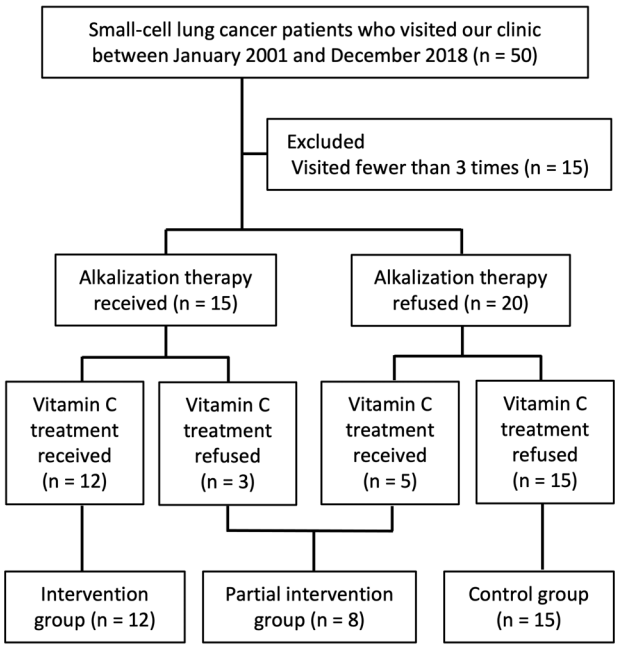

Figure 1. *Flowchart of this study. Flowchart showing the number of patients included in the study groups.*

Intervention methods. Alkalization therapy was defined as a combination of an alkaline diet and bicarbonate therapy. An alkaline diet was meals comprising a large amount of vegetables and fruit, and minimal meat and dairy products. All patients who received alkalization therapy were instructed to take at least 400 g of fruit and vegetables a day and not to take any meat and dairy products, and they recorded their daily meals for at least the first 4 weeks from the start of the alkaline diet. Their records were reviewed to confirm whether the meals were appropriate or not by a doctor or nurse at every visit, and they were given advice according to their records, but the actual diet was decided by the patients at their homes. Patients who received alkalization therapy also received oral bicarbonate (3.0–5.0 g/day). Patients who agreed to receive vitamin C treatment were given vitamin C (25-50 g/day by infusion every 1 or 2 weeks). Patients were allowed to receive all appropriate concomitant chemotherapies in addition to the alkalization therapy and intravenous vitamin C treatment.

Assessment procedures. The OS from the time of diagnosis in the intervention group and control group were calculated. Urine pH data in both groups were also collected at the patients' regular visits, which were at least once every 2 months, and up to twice a month.

Statistical analyses. Mean values of urine pH for each patient were calculated from all data on the pH of urine samples collected from each patient's first visit to Karasuma Wada Clinic until March 31, 2021. Mean urine pH values were compared between the intervention group and the control group using unpaired t-test. The OS from the time of diagnosis for the intervention and the control groups was compared using Kaplan–Meier estimates. Standard deviations of mean dataset values were calculated. All *p*-values were

Table I. *Patient characteristics*.

		Intervention	Control	Partial intervention
No. of patients	Total	12	15	8
Age, years	Mean (range)	72.7 (64-81)	65.2 (52-79)	67.9 (47-80)
Gender, n	Men	10	11	8
	Women	2	4	0
Alkalization therapy/vitamin C, n	Yes/yes	12	0	0
	Yes/no	0	0	3
	No/yes	0	0	5
	No/no	0	15	0
Clinical stage, n	Limited disease	7	8	4
	Extensive disease	5	5	4
	Unknown	0	2	0
Surgery, n	Yes (postoperative recurrence)	2	0	1
	No	10	15	7
First-line chemotherapy, n	Carboplatin plus etoposide	9	7	5
	Cisplatin plus etoposide	0	2	2
	Carboplatin plus irinotecan	0	1	0
	Cisplatin plus irinotecan	1	0	0
	Amrubicin	0	0	1
	Unknown	2	5	0
Radiation, n	Yes	5	6	1
	No	7	9	7
Prophylactic cranial irradiation, n	Yes	2	2	1
	No	10	13	7

two-sided and a p-value of less than 0.05 was considered to indicate a statistically significant difference between two groups. All statistical analyses were performed with EZR (version 1.54; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface that is a modified version of R (The R Foundation for Statistical Computing, Vienna, Austria) (19); more precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics. Fifty patients with SCLC visited Karasuma Wada Clinic between January 1, 2011 and December 31, 2018. Of these patients, 15 who visited fewer than three times were excluded. Of the 35 remaining patients, 12 were assigned to the intervention group, 15 were assigned to the control group, and eight were assigned to the partial intervention group. The mean age at diagnosis of patients in the intervention group was 72.7 years (range=64-81 years), and in the control group was 65.2 years (range=52-79). Five patients out of 12 in the intervention group, and five out of 15 in the control group had extensive disease. Two patients out of 12 in the intervention group had postoperative recurrent disease, and no patients in the control group underwent surgery. Regimens of the first-line chemotherapies that the patients received in both groups did not differ remarkably. Patient characteristics are shown in Table I.

Urine pH analysis. The mean urine pH during the period from each patient's first visit until March 31, 2021 for the intervention group and the control group are shown in Figure 2. The mean urine pH of the intervention group was significantly higher than that of the control group (7.32±0.45 *vs*. 6.44±0.74; $p<0.005$).

Overall survival. The median OS from the time of diagnosis for the intervention group was 44.2 months (n=12, 95% confidence interval=22.0–not reached) as compared with 17.7 months for patients in the control group (n=15, 95% confidence intervaI=13.5–not reached; $p<0.05$). The Kaplan–Meier curves of both groups are shown in Figure 3.

Discussion

SCLC is a highly malignant tumor with a rapid growth rate and early metastasis, and is one of the most difficult tumors to treat. The 5-year relative survival rate of patients who were diagnosed as having SCLC between 2009 and 2011 in Japan was 17.3% (1). In the present retrospective study, we demonstrated that the median OS of patients with SCLC who received a combination of alkalization therapy and intravenous vitamin C treatment together with chemotherapy was significantly longer than that of those who received only chemotherapy. The combination of alkalization therapy and

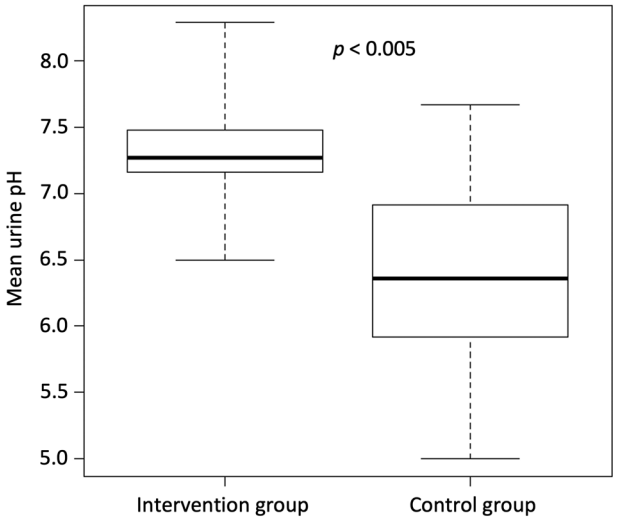

Figure 2. *Urine pH in patients of the intervention and the control groups for the study period. The mean urine pH of the intervention group (n=12) and the control group (n=12) are shown. The lines indicate the median values, the error bars indicate the maximum and minimum values, and the boxes indicate the values between the upper and the lower quartiles.*

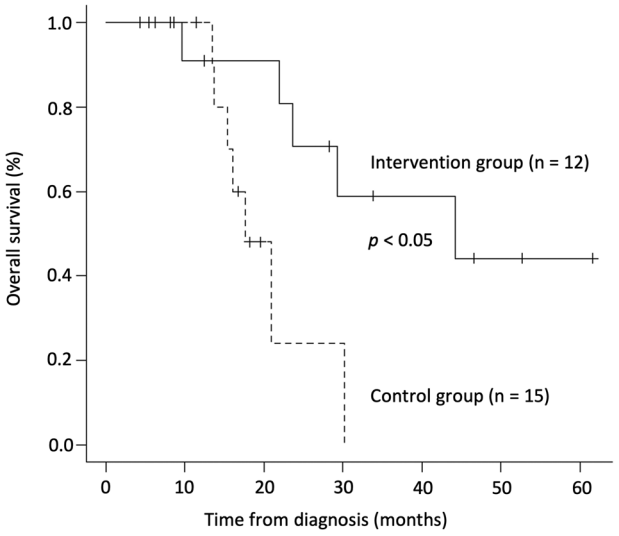

Figure 3. *Overall survival of the intervention and control groups. Kaplan–Meier curves of the overall survival from diagnosis of small-cell lung cancer in patients in the intervention group and the control group are shown.*

intravenous vitamin C treatment may exert synergetic effects that contribute to the favorable outcomes of patients with SCLC, because the median OS was not prolonged in those who received only alkalization therapy or only intravenous vitamin C treatment together with chemotherapy. However, we were not able to compare the median OS of the partial intervention group and the control group in this study, owing to the small number of patients who received only alkalization therapy or only intravenous vitamin C treatment in addition to chemotherapy, and hence further investigation is needed.

Similar to our previous studies (10-12), a significant increase in mean urine pH was observed in patients who received alkalization therapy and intravenous vitamin C treatment compared with the control group in the present study. The effects of diet on the acid–base balance can be predicted through calculating the potential renal acid load of foods, and it is known that fruit and vegetables have an alkalizing effect, and meat and dairy products have an acidifying effect on urine pH (20). Acid from the daily diet is neutralized or 'stored' within the body, and also accumulates within cells, and results in a decrease in the level of serum bicarbonate (21). A clinical study has shown the safety and tolerability of the long-term consumption of bicarbonate (0.5 g/kg/day, *i.e.*, 25 g/50 kg body weight), and bicarbonate is also known to have buffering effects and to increase urine pH levels (22). Although the effects of chemotherapeutic drugs on urine pH are not well known, a clinical study reported that cisplatin did not affect urine pH (23). We believe empirically that without alkalization therapy, chemotherapy with vitamin C does not affect urine pH; however, we have no clinical data regarding this point, and therefore further studies are required to clarify the effects of other chemotherapeutic drugs or intravenous vitamin C on urine pH. Consequently, we suggest that alkalization therapy, which consists of an alkaline diet and bicarbonate, has an alkalizing effect on the body and results in an increase in urine pH.

Although the association between the pH of the tumor microenvironment and urine pH was not clarified in this study, computer simulation studies reported that bicarbonate consumption leads to an increase in the pH of the tumor microenvironment (24, 25). Moreover, an *in vivo* study demonstrated that bicarbonate administration in mouse models of metastatic breast cancer increased the pH of tumor cells and resulted in the suppression of cancer progression (8). Neutralization of the acidic pH of the extracellular tumor microenvironment has been shown to lead to improvements in multi-chemotherapeutic drug resistance in several *in vivo* and *in vitro* studies (4, 9, 26, 27). It was reported that in an acidic environment, weak-base chemotherapeutic drugs are positively charged and become trapped in extracellular compartments, leading to a reduction in their cellular uptake and efficacy (28-30). In addition, an acidic tumor microenvironment is also associated with the mechanisms of

multidrug efflux. Firstly, P-glycoprotein, which is a multidrug transporter, is activated and expressed in an acidic environment, and results in a decrease in the level of chemotherapeutic drugs in the body (31, 32). Secondly, an increase in the number of exosomes is observed in an acidic tumor microenvironment, which assist in removing chemotherapeutic drugs from cancer cells (33, 34). In the present study, a prolonged median OS and increased urine pH was observed in patients in the intervention group compared with those in the control group. Similarly, our previous study demonstrated that a urine pH of higher than 7.0, or a urine ΔpH of more than 1.0 was significantly associated with prolonged OS in patients with advanced pancreatic cancer compared with a urine pH of 7.0 or lower, or a urine ΔpH of 1.0 or less (11, 12). Therefore, we believe that alkalization therapy has a neutralizing effect on the acidic tumor microenvironment, and is associated with favorable outcomes of patients with SCLC.

In this study, a prolonged median OS was observed in patients with SCLC who received both alkalization therapy and intravenous vitamin C treatment together with chemotherapy, compared with those who received only chemotherapy. Although clinical reports on intravenous vitamin C as a supplementary treatment for various cancer therapies are increasing, there are still very few reports regarding SCLC (13-16). SCLC typically occurs in heavy smokers and is characterized by poor patient survival owing to its aggressive growth and frequent metastases. About 90% or more patients with SCLC have somatic mutations in the tumor suppressor gene *TP53* which are associated with the overexpression of mutant P53 protein in tumor cells (35). The P53 protein binds to glucose-6-phosphate dehydrogenase, which is the first and rate-limiting enzyme of the pentose phosphate pathway and suppresses the overactivation of glycolysis. On the other hand, mutant P53 proteins lack this glucose-6-phosphate dehydrogenase-inhibitory activity, which may result in activated glycolysis *via* the pentose phosphate pathway (36). Activation of aerobic glycolysis is an essential characteristic of cancer cell metabolism, and hence the regulation of activated glycolysis may be a potential therapy for cancer (6). Vitamin C is transported into cancer cells *via* the glucose transporter, is oxidized to DHA, and then DHA inhibits glyceraldehyde 3-phosphate dehydrogenase, which may result in the suppression of activated glycolysis, particularly in cancer cells with high glycolytic metabolism (17). Therefore, intravenous vitamin C treatment may have favorable effects on the treatment outcomes of patients with SCLC.

We acknowledge that this study has several limitations. Firstly, this was a retrospective study analyzing a small number of patients from a single center. Secondly, we recognize that the timing of the start of alkalization therapy and intravenous vitamin C treatment from the time of diagnosis in the intervention group was not consistent and we were not able meticulously to control the details of the patients' daily diet. Therefore, a prospective randomized study is necessary to further clarify the effects of the combination of alkalization therapy and intravenous vitamin C treatment. Moreover, we acknowledge that alkalization therapy may have some other potential effects besides an alkalization effect. An alkaline diet with more vegetables and fruit and less meat and dairy products may result in caloric restriction and anti-inflammatory effects in the body, which may affect cancer metabolism. Hence, methods to measure the pH of the tumor microenvironment, such as acido-chemical exchange saturation transfer magnetic resonance imaging, which can measure the extracellular pH of the tumor microenvironment using the ratio of two pH-dependent signals from such imaging may be useful for clarifying the association between the combination of alkalization therapy plus intravenous vitamin C treatment and pH changes of the tumor microenvironment (37, 38).

Conclusion

We demonstrated that the combination of alkalization therapy and intravenous vitamin C treatment results in an increase in the urine pH of patients with SCLC, and may improve their outcomes from chemotherapy treatment. An alkaline urine pH may hence be associated with favorable outcomes in patients with SCLC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest associated with this study.

Authors' Contributions

Reo Hamaguchi performed the literature review, analyzed the data, and wrote the article. Ryoko Narui and Hiromasa Morikawa performed the acquisition of data. Hiromi Wada supervised the study. All Authors conceived and designed the study and gave final approval for publication.

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