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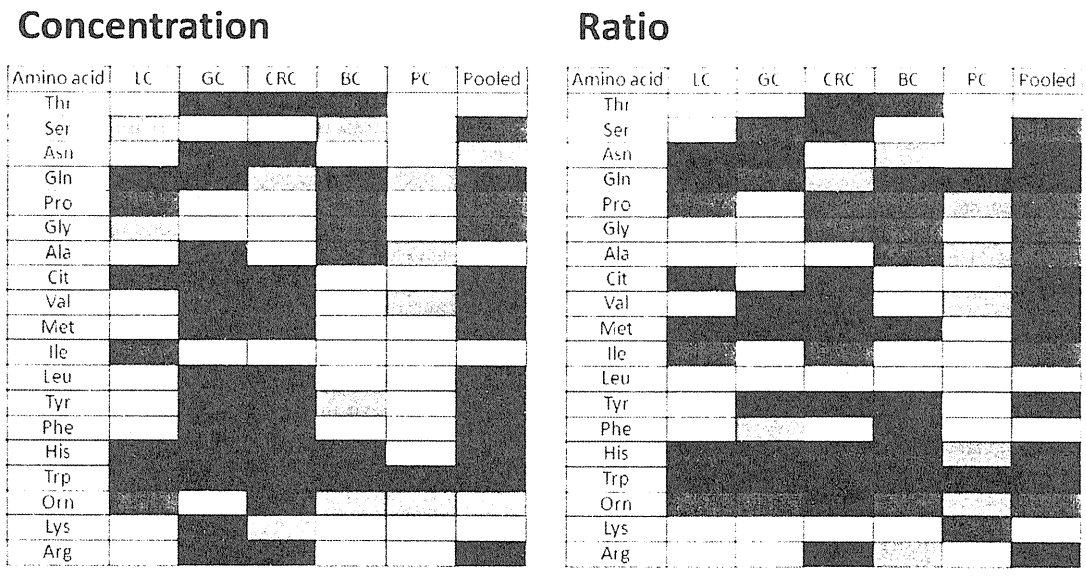
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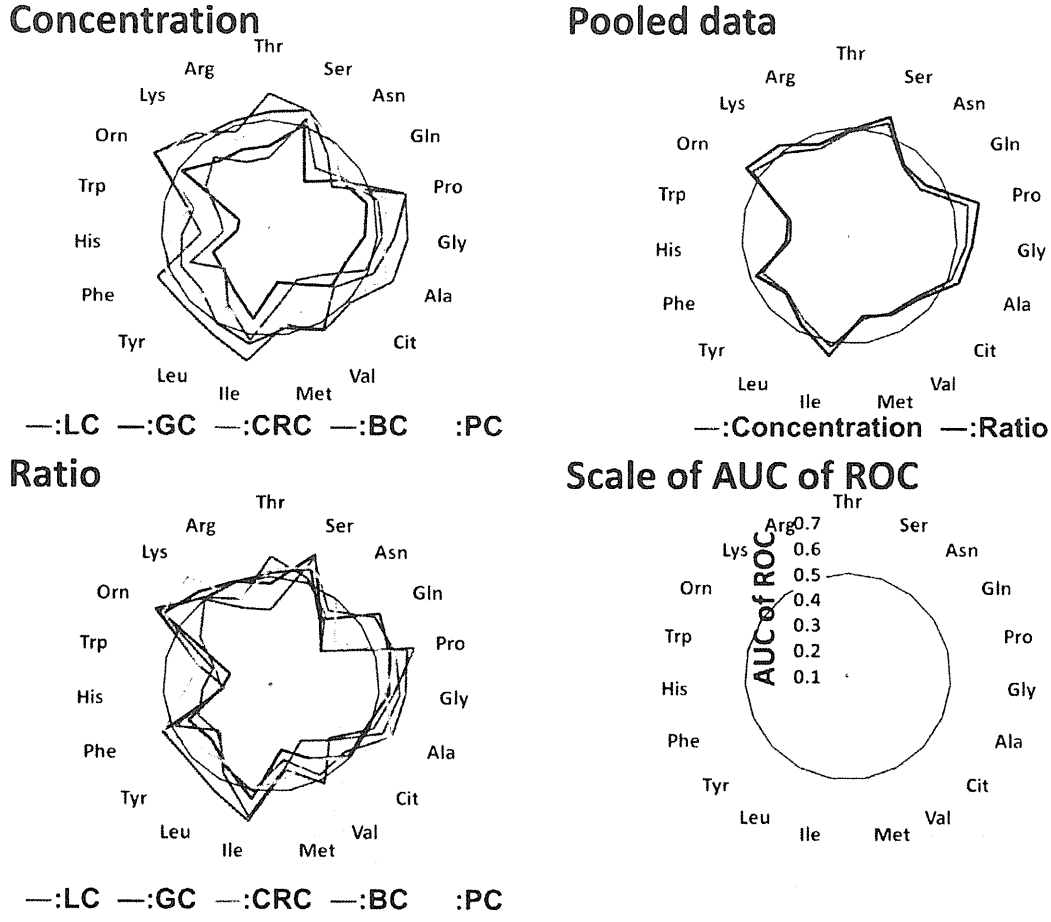
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AUC of ROC
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—:LC —:GC —:CRC —:BC :PC
—:Concentration —:Ratio

Figure 2. PFAA profiles of cancer patients. The results of the Mann-Whitney *U*-test (A) and receiver-operator characteristic (ROC) curve analysis (B) are indicated. A. Colored cells indicate that the concentration or ratio is increased in cancer patients at $p<0.001$ (red), $p<0.01$ (orange), and $p<0.05$ (pink), and decreased in cancer patients at $p<0.001$ (blue), $p<0.01$(sky blue), and $p<0.05$ (light blue), respectively. B. Axes show the AUC of ROC for each amino acid to discriminate patients from controls. Concentrations and ratios of each cancer patient and the pooled data set are indicated, respectively. Black bold lines indicate the point where the AUC of ROC = 0.5.
doi:10.1371/journal.pone.0024143.g002

detected by the univariate analysis alone. Indeed, Spearman's partial correlation coefficient between Val and cancer (or not) was −0.127 ($p<0.001$), while the correlation coefficient between these two factors was 0.035 (not significant). Therefore, this suggested that the obtained LDA model reflected the metabolic network of PFAAs, which were not apparent thorough univariate analysis.

Because the obtained results may have been over-optimized, LOOCV was carried out to generate an unbiased analysis. This produced AUCs similar to those obtained for LDA, suggesting that there was no obvious over-optimization in the obtained LDA models (Table 3 and Table S7).

Subgroup analyses of divided data sets according to cancer stage, including corresponding controls, were then performed to assess the ability of PFAA profiles to distinguish between stages of cancer for each type of disease. In any stage of each cancer, the AUC of ROC was found to be higher than 0.75, suggesting that the obtained LDA models would thus be expected to be effective in detecting early as well as advanced stage cancers (Table 3 and Table S7).

The discrimination abilities for all cancer patients were also evaluated. The AUCs of ROC for both concentrations and ratios were 0.796 (95% CI: 0.779~0.814) and 0.785 (95% CI: 0.767~0.803), respectively (Table 3 and Table S7). Notably, most of the 19 amino acids were statistically selected for these discriminations: 16 for the concentrations and 12 for the ratios. Even using a rough classification, regardless of the type of cancer, it was possible to discriminate between patients and controls with high accuracy, and the overall contributions of numerous amino acids might reflect the large-scale characteristic changes associated with cancer metabolism.

A c-logistic analysis using matching factors (gender and age) was performed for each data set to evaluate and correct for potential confounding factors. Note that we used the combinations of amino acids obtained from the LDA models as explanatory variables. Although the c-logistic analysis was performed using all of the significant variables identified by the univariate analysis, the amino acids identified in the LDA were utilized to correct for potential confounding factors more adequately (data not shown). Both the levels of significance (Table 2 and Table S6) and the discrimination abilities (Table 3 and Table S7) were not significantly altered by correcting for the potentially confounding factors, suggesting that these results were independent of gender and age effects.

To evaluate patients with non-neoplastic diseases, the PFAA profiles of colonic polyp patients were substituted into the LDA model for CRC. Most of the colonic polyp patients (31/34, 91.2%) were classified into the control group for the concentrations and ratios of both models, suggesting that the obtained models could discriminate CRC patients specifically.

Discrimination between cancer types by PFAA profiles

In addition to differentiating between patients with each type of cancer and the controls, discrimination among patients within each cancer group was also performed by separating all the cancer patients into each disease subtype according to gender. This was done because the results of the present analyses identified changes in PFAA profiles that were common to all types of cancer as well as those specific to individual cancers.

The accuracies of all discriminant analyses using amino acid concentrations as explanatory variables were close to or better than 50% both in male patients (Table 4) and female patients (Table 5) data set. The discrimination accuracy among cancer patients was less than that between patients and controls. Six amino acids (Gly, Cit, Val, Tyr, Trp, and Arg) were commonly selected in these analyses, regardless of gender (data not shown). An additional six amino acids (Gln, Met, Leu, His, Orn, and Lys) were selected in the male patient data set, and four (Thr, Ser, Ile, and Phe) were selected in the female patient data set (data not shown). Five of the 16 amino acids listed above were selected in the discrimination between patients and controls, while the remainder might have been responsible for the characteristic features of each cancer.

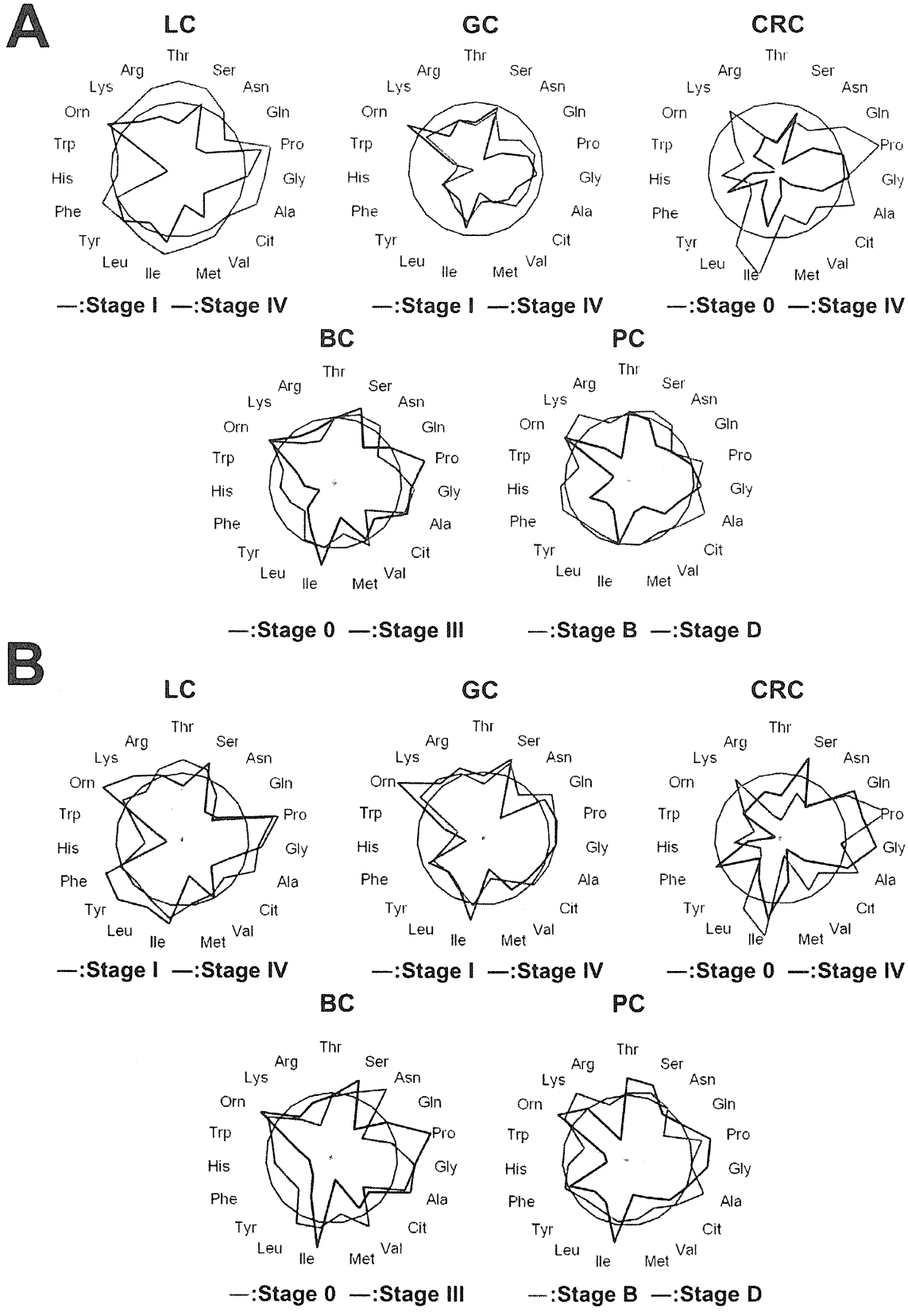
The accuracies were similar between the analyses using ratios as explanatory variables and those using concentrations both in male patients (Table S8) and female patients (Table S9). Seven amino acids (Gln, Cit, Val, Tyr, Trp, Lys, and Arg) were commonly selected regardless of gender in these analyses (data not shown). An additional four amino acids (Ala, Met, Leu, and His) were selected in the male patient data set, and four (Thr, Ser, Ile, Orn) were selected in the female patient data set (data not shown). Five amino acids (Cit, Val, Tyr, Trp, and Arg) from each set were selected for both explanatory variables, suggesting that the changes to the respective PFAAs were specific to certain types of cancer.

LOOCV was also carried out and resulted in similar accuracies for the discrimination analyses, suggesting that there was no obvious over-optimization in the obtained models (Table 4, Table 5, Table S8 and Table S9).

Discussion

The present study demonstrated the use of PFAA profiling as a focused metabolomics approach for the early detection of patients with any of five types of cancer. Combining novel analytical techniques and both univariate and multivariate statistical analyses, previously unknown aspects of amino acid metabolism in humans have been revealed. The sample size in the present study was considerably larger than those reported previously [25,29,30], and provided sufficient statistical power to test the robustness of PFAA profiling for cancer diagnosis. We also demonstrated the possibility of detecting cancers, both specifically and broadly, using multivariate analysis to compress the PFAA profile data, even for patients with early stage cancer.

In the previous studies, the alterations in PFAA profiles in cancer patients sometimes seem inconsistent[22,23,24,25,26,27,28,29,30], and some discrepancies existed between our current study and those reported in the literature [25]. This discrepancy may be due not only to sample size and the varying predominance of early stage cancers but also to some other factors such as amino acid measurement methods. On the other hand, alterations in the PFAA profiles in our present study were consistent with the results of our previous studies, in which samples were collected from a single medical institute [29,30]. Furthermore, there are also many similarities between our results and those of previous studies. For example, decreases in His and Gln levels, which have been observed broadly in previous reports, and increases in Pro and Ala levels in BC are consistent with our findings [25].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—:Stage 0 —:Stage III
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GC
CRC
—:Stage I —:Stage IV
—:Stage I —:Stage IV
—:Stage 0 —:Stage IV
BC
PC
—:Stage 0 —:Stage III
—:Stage B —:Stage D

Figure 3. PFAA profiles of early- and advanced-stage cancer patients. The axes show the AUC of ROC for each amino acid for discriminating patients from controls. A. Comparison of concentrations of cancer patients and controls. B. Comparison of ratios of cancer patients and controls. Scale as described for Figure 2. For LC, GC, CRC, and BC, cancer stages were determined according to the International Union Against Cancer TNM Classification of Malignant Tumors, 6th edition [38], and for PC, cancer stages were determined according to Jewett staging system [39].
doi:10.1371/journal.pone.0024143.g003

Cancer is expected to become the leading cause of death worldwide within a few years. Therefore, it is crucial that methods for the prevention, early detection, and treatment of cancers should be implemented to reduce mortality. Various screening methods have been established for the cancers included in our study. However, the high specificity of these methods means that subjects must undergo each screening examination separately, which can be expensive and time consuming. These examinations can also impose a physical and/or mental burden upon subjects, which can lead to avoidance. By contrast, the method described in the present study involves a relatively simple plasma assay and imposes a low physical burden on subjects. This method could also be used as versatile health assessment as other diseases in which PFAA profiles can be altered, such as diabetes[18], hepatic failure[19], and renal failure[21], can also be evaluated.

It should be noted that the models derived from this case-control study could not be used directly to make further observations or predictions, despite providing a preliminary demonstration of the potentially high value of this method for cancer discrimination. Further investigations, including model construction and validation using cohorts with larger sample sizes, are in progress to clarify the clinical utility of this approach. Moreover, the possibility of continuous PFAA profiling as a means to determine prognosis after surgery or chemotherapy is also being investigated.

Our investigation demonstrated two types of alterations in PFAA profiles of cancer patients: those in a limited set of amino acids reflecting metabolic changes common to many cancers; and those in a larger group of amino acids representing metabolic characteristics specific to each cancer. Alterations in PFAA profiles were observed even in patients with early-stage cancer, most of whom had no apparent symptoms. This strongly suggested that the alterations in PFAA profiles identified in the current study were independent of the effects of poor nutrition caused by tumor progression.

Many previous reports have shown that metabolism, including that of amino acids, is notably altered in cancer cells [3,13,40] and that changes in PFAA profiles can also occur [22,24,25,26,27,28,29,30], especially in cachexic patients with advanced cancer [23,25]. Among whole metabolites, amino acids have been frequently identified as having associations with cancer in other studies [10,13,41,42,43]. The current study demonstrated that mechanisms other than malnutrition can drive the changes in PFAA profiles.

Besides cancer-dependent malnutrition, significant decreases in PFAA concentrations and various indicators of nutritional status such as BMI and serum albumin levels are observed in cancer-independent cachexia [44,45,46]. In the present study, no apparent decreases in those indicators were observed, strongly suggesting that alterations in PFAA were also independent of nutritional status mediated by factors not related to cancer.

Table 2. Variables incorporated into LDA and c-logistic models using concentrations as explanatory variables.

Amino acid	LC		GC		CRC		BC		PC		Pooled	
	LDA	C-logit	LDA	C-logit	LDA	C-logit	LDA	C-logit	LDA	C-logit	LDA	C-logit
Thr							+++	+++			+++	+++
Ser	+++	+++			+++	+++					+++	+++
Asn												
Gln	−−−	−−−					−−−	−−−	−−−	−−−	−−−	−−−
Pro	+++	+++									+++	+++
Gly							+++	++				
Ala					+++	+++	+++	+++	+++	+++	+++	+++
Cit	−−−	−−−	−−−	−							−−−	
Val	−−−	−	−−−	−−	−−−	−−−			−−−	−−−	−−−	−−−
Met											−−−	−−−
Ile	+++	+++	+++	+	+++	+++			+++	++	+++	+++
Leu					+++	+++					+++	++
Tyr					−−−	−−−	−−−	−−				
Phe	+++	+++									+++	+++
His	−−−	−−−	−−−	−−−	−−−	−−−					−−−	−−−
Trp	−−−	−−−	−−−	−−−	−−−	−−	−−−	−−−	−−−	−−−	−−−	−−−
Orn	+++	+++					+++	+++	+++	+++	+++	+++
Lys			+++	+++	+++	+++			+++	+++	+++	+++
Arg					−−−	−−−			−−−	−−−	−−−	−−−

+, ++, +++: positive coefficients in the model.
−, −−, −−−: negative coefficients in the model.
+,−: $p<0.05$, ++,−−: $p<0.01$, +++,−−−: $p<0.001$.
doi:10.1371/journal.pone.0024143.t002

Table 3. Discrimination performance of LDA and c-logistic models using concentrations as explanatory variables.

Model	Subjects		LC	GC	CRC	BC	PC	Pooled
LDA	All	AUC	0.802	0.849	0.874	0.778	0.783	0.796
		CI	(0.766~0.836)	(0.816~0.882)	(0.842~0.906)	(0.741~0.815)	(0.740~0.826)	(0.779~0.814)
	LOOCV	AUC	0.792	0.845	0.868	0.769	0.767	0.793
	Stage 0 patients	AUC	-	-	0.903	0.813		
		CI			(0.807~1.00)	(0.726~0.900)		
	Stage I patients	AUC	0.752	0.859	0.859	0.754		
		CI	(0.698~0.805)	(0.820~0.898)	(0.800~0.918)	(0.692~0.817)		
	Stage II(B) patients	AUC	0.870	0.829	0.921	0.786	0.764	
		CI	(0.772~0.969)	(0.726~0.933)	(0.877~0.954)	(0.727~0.847)	(0.710~0.819)	
	Stage III(C) patients	AUC	0.844	0.834	0.817	0.755	0.777	
		CI	(0.780~0.908)	(0.748~0.920)	(0.743~0.892)	(0.621~0.889)	(0.669~0.885)	
	Stage IV(D) patients	AUC	0.901	0.843	0.950	-	0.873	
		CI	(0.837~0.966)	(0.734~0.951)	(0.895~1.00)		(0.771~0.974)	
C-logit	All	AUC	0.806	0.850	0.876	0.776	0.786	0.798
		CI	(0.771~0.841)	(0.816~0.883)	(0.845~0.907)	(0.739~0.812)	(0.743~0.829)	(0.780~0.815)

doi:10.1371/journal.pone.0024143.t003

Nevertheless, it remains unclear how the metabolic changes occurring in cancer patients affect the PFAA profile of the whole body, even in patients with early-stage tumors. To clarify the relationship between carcinogenesis and changes in PFAA profiles, we are further investigating the contribution of local effects caused by cancer cell metabolism and the systemic responses of the immune system against tumors or factors released by cancer cells.

Changes in metabolism can be detected in cancer cells even in early-stage patients. Hirayama *et al.* reported no significant correlation between the levels of cancer cell metabolites, including several amino acids, and the tumor stage [13]. The metabolism of Trp is of particular interest because it was identified as one of the most important amino acids in relation to cancer progression in our study. Overexpression of indoleamine-2,3- dioxygenase (IDO), the first enzyme in the kynurenine Trp metabolism pathway in humans, has been reported in cancer cells [47]. IDO is induced in many different tumors and has been suggested to play a role in cancer-mediated evasion of the immune system [47,48,49,50].

Arg, Orn, Cit, and Pro are known to be closely related to immune function. For example, Qiu *et al.* reported an association between the urea cycle and metabolic alterations in CRC patients and found no correlation between the metabolite profile and cancer progression [43]. Cancer cells also release factors that can alter general physical conditions. For example, the transcriptional regulatory molecule high-mobility group B1 (HMGB1) was recently shown to regulate cancer-cell tumorigenesis, expansion, and invasion [51,52,53].

Further elucidation of these mechanisms might allow for the development of both static and dynamic models of carcinogenesis through system analysis [31]. Recently, computer-aided studies have been reported that integrate hierarchical 'omics' datasets for the systemic understanding of metabolic phenotypes to reconstruct the regulatory network from physiological data by means of system analysis. System analysis of cancer patients based on whole body amino acid metabolism could reveal information concerning the nature of a disease and help to establish strategies for its prevention, early detection, prognosis, monitoring, and treatment.

In contrast to many similar efforts to detect biomarkers of disease as single specific molecules (DNA, microRNA, proteins, peptides, or metabolites) in peripheral blood, our approach was to focus on the metabolic status, which is indicative of multivariate function, using non-specific metabolites. Therefore, we believe that our method is superior to those used in other studies, both in versatility and efficiency, because only one amino acid measurement can be applied for detection of various disease states (i.e., renal failure, hepatic failure, and nutritional status).

Table 4. Multiclass discriminant analyses of male cancer patients using concentrations as explanatory variables.

		Patients with:			
		LC	GC	CRC	PC
Discriminated as:	LC	**72(69)**	*19(22)*	*12(13)*	*26(26)*
	GC	*18(19)*	**58(52)**	*16(17)*	*25(25)*
	CRC	*13(14)*	*25(28)*	**71(69)**	*16(17)*
	PC	*22(23)*	*24(24)*	*15(15)*	**67(66)**
	Total	125	126	114	134
	Accuracy	**57.6%(55.2%)**	**46.0%(41.3%)**	**62.3%(60.5%)**	**50.0%(49.3%)**

The numbers in the blanket indicate the results of LOOCV.

doi:10.1371/journal.pone.0024143.t004

Table 5. Multiclass discriminant analyses of female cancer patients using concentrations as explanatory variables.

		Patients with:			
		LC	**GC**	**CRC**	**BC**
Discriminated as:	LC	**41(37)**	*4(6)*	*8(11)*	*43(44)*
	GC	*13(14)*	**40(38)**	*15(16)*	*30(30)*
	CRC	*6(8)*	*13(13)*	**52(47)**	*17(17)*
	BC	*15(16)*	*16(16)*	*10(11)*	**106(105)**
	Total	75	73	85	196
	Accuracy	**54.7%(49.3%)**	**54.8%(52.1%)**	**61.2%(55.2%)**	**54.1(53.6%)**

The numbers in the blanket indicate the results of LOOCV.
doi:10.1371/journal.pone.0024143.t005

Supporting Information

Figure S1 PFAA profiles of cancer patients stratified by progression stage. The axes show the AUC of ROC for each amino acid for discriminating patients from controls. A. Comparison of concentrations of cancer patients and controls. B. Comparison of ratios of cancer patients and controls. Scale as described for Figure 2. For LC, GC, CRC, and BC, cancer stages were determined according to the International Union Against Cancer TNM Classification of Malignant Tumors, 6th edition [38], and for PC, cancer stages were determined according to Jewett staging system [39].
(TIF)

Table S1 Detailed demographic and clinical characteristics of subjects. a: $p<0.05$, c: $p<0.001$ *: For LC, GC, CRC, and BC, cancer stages were determined according to the International Union Against Cancer TNM Classification of Malignant Tumors, 6th edition [38], and for PC, cancer stages were determined according to Jewett staging system [39].
(XLS)

Table S2 PFAA profiles of cancer patients and controls.
(XLS)

Table S3 AUCs of ROC of each amino acid concentration for discrimination for cancer patients from controls.
(XLS)

Table S4 AUCs of ROC of each amino acid ratio for discrimination for cancer patients from controls. AUCs were calculated using all patients and controls, and patiens and matched controls stratified by cancer stage.
(XLS)

Table S5 Significance values for PFAA profiles for each data set by two-way ANOVA for the effects of cancer existence and other parameters. Column headings indicate Mann-Whitney U-test of cancer existence (None), two-way ANOVA for the effects of cancer existence and gender (Gender), cancer existence and age (Age), and cancer existence and smoking status (Smoking).
(XLS)

Table S6 Variables incorporated into LDA and c-logistic models using ratios as explanatory variables. +, ++, +++: positive coefficients in the model −, −−, −−−: negative coefficients in the model +,−: $p<0.05$, ++,−−: $p<0.01$, +++,−−−: $p<0.001$.
(XLS)

Table S7 Discrimination performance of LDA and c-logistic models using ratios as explanatory variables.
(XLS)

Table S8 Multiclass discriminant analyses of male cancer patients using ratios as explanatory variables. The numbers in the blanket indicate the results of LOOCV.
(XLS)

Table S9 Multiclass discriminant analyses of female cancer patients using ratios as explanatory variables. The numbers in the blanket indicate the results of LOOCV.
(XLS)

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Author Contributions

Conceived and designed the experiments: YM HY MY NO. Performed the experiments: MH AG MA TI T. Miura NS EB HK FI MM II AC FO HM OT T. Mitsushima MY NO. Analyzed the data: YM AI KH. Contributed reagents/materials/analysis tools: HM. Wrote the paper: YM AI KH.

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委員会報告

模擬患者・標準模擬患者（SP）養成のカリキュラム

第16期日本医学教育学会教材開発・SP委員会
志村　俊郎[*1, 1)]　吉井　文均[*2, 2)]　吉村　明修[*1]
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要　旨：
1）第16期教材開発・SP委員会は，全国の実態調査等に基づき，基本的な模擬患者・標準模擬患者の養成カリキュラムを策定した．
2）このカリキュラムでは，SPとなるために修得すべき必須項目として，対人コミュニケーション，医学教育におけるSP参加型教育，医学教育における医療面接を示した．
3）医療面接における必須項目として，基本的事項，シナリオの理解，役作りと演技，フィードバックと評価を示した．
4）養成されたSPが実際の教育場面に参加するに当たっては，SPを養成した施設あるいは組織において適切な評価を行うとともに，その評価方法が明示される必要がある．
キーワード：模擬患者・標準模擬患者，カリキュラム，対人コミュニケーション，SP参加型教育，医療面接

Training Curriculum for Simulated and Standardized Patients: The 16th Medical Simulation Committee of the Japan Society for Medical Education

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Summary：
1. The basic training curriculum for simulated and standardized patients (SPs) was provided by the 16th Medical Simulation Committee based upon a nationwide field survey that was conducted by the committee in 2009 and other data.

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2. The curriculum consists of 3 essential programs: interpersonal communication, medical education involving SPs, and the medical interview.
3. The medical interview program was composed of basic issues, comprehension of scenarios, acting role and performance, and feedback and assessment.
4. The training facilities or institutions were recommended to properly assess the performance quality of SPs in the educational setting by means of a specific and clearly defined evaluation method.
Key words: simulated and standardized patients, curriculum, communication, medical education involving standardized patients, medical interview

1. 緒　言

日本における組織的なSP*養成は1992年に始まり，すでに19年が経過した．その間，医学教育におけるコミュニケーション，医療安全，生命倫理など，SPが参加する教育機会は増加し，研修医教育，歯科医学教育，薬学教育など他の分野への展開などにより，今後いろいろな教育場面でSPが必要とされることが予想される[1]．また，共用試験OSCEにおける標準模擬患者の演技の標準化，Advanced OSCEの導入と医療面接における標準模擬患者の演技の標準化，わが国の実情に即した身体診察SPの導入などの問題点が課題として指摘されている[1]．

第16期教材開発・SP委員会は，「模擬患者・標準模擬患者養成および参加型教育に関する実態調査」を実施し，学内，学外にかかわらないSP養成の推進，SP養成の標準化の必要性を提言した[2]．そして，医学教育におけるSPの意義・役割を社会，医学部の教員・学生等が理解し，SPが参加する教育が医学部教育に益々寄与するために，SPとしての活動目的を明示するとともに，SP養成のために到達目標，行動目標が示されたカリキュラムを策定する必要性を示した．

SPは日本における医学教育を理解し，各医学部・医科大学の教育理念・教育方針に賛同し，患者のための医療を目指す医師を育てる人材として協力するものである．医療面接および試験等のプログラムにおいてSPとして患者役を果たし，医学生，研修医，医師およびその他の医療従事者等の技術およびコミュニケーション能力を向上させて信頼される医療人を育てることを目的とする．SPは患者役としての能力向上のために必要な知識と技術を習得し，常に自己研鑽に励むことが望まれる[3,4]．

第16期教材開発・SP委員会は，全国の実態調査等に基づき，一般的なSP参加型教育のために模擬患者・標準模擬患者の養成カリキュラムを策定した．このカリキュラムは，医学部教育におけるSP養成を目的としたものであるが，研修医教育，歯科医学教育，薬学教育など他の分野にも応用できる基本的な内容とした．身体診察，身体援助に関わるSPの養成については，今後の課題とする．

なお，共用試験OSCEの標準模擬患者については，医療系大学間共用試験実施評価機構が別途定めるものであるが，本カリキュラムは参考になるものと考えている．

SPとなるために修得すべき必須項目として，Ⅰ．対人コミュニケーション，Ⅱ．医学教育におけるSP参加型教育，Ⅲ．医学教育における医療面接を掲げ，SP活動の主体となる項目Ⅲでは，医療面接の基本的事項，医療面接のシナリオの理解，役作りと演技，フィードバックと評価について習得すべき到達目標を示した．このカリキュラムに基づいて養成されたSPが実際の教育場面に参加するに当たっては，SPを養成する施設あるいは組織において適切な評価を行うとともに，その評価方法が明示される必要がある．

*註1　なお，本文中の模擬患者・標準模擬患者は一括してSPとして表記し，模擬患者，標準模擬患者を区別する必要がある場合には，それぞれ模擬患者，標準模擬患者と記載した．

表1　対人コミュニケーションの技法

- 開放型質問，閉鎖型質問
- 沈黙
- うながし
- 繰り返し（オウム返し）
- 明確化，言い換え
- 要約
- 確認，質問のチャンスを与える
- 声かけ，社交的な会話など

表2　医療面接における患者－医師関係のコミュニケーションの特徴

- 医療面接の3つ役割軸モデル（情報収集，ラポール形成，情報提供）
- 医療面接における導入と締めくくり
- ラポールの形成
- 主訴に関する必須7項目（部位，性状，程度，経過，起きる状況，増悪寛解因子，随伴症状）
- 解釈モデル
- システム・レビュー
- 既往歴
- 家族歴

2. カリキュラム

Ⅰ. 対人コミュニケーション

SPが医学教育に協力するために，SPは基本的なコミュニケーションについて理解し，良好なコミュニケーションができる．

Ⅰ-1　基本的な対人コミュニケーション

Ⅰ-1-1　対人コミュニケーションの基本事項について説明できる（認知）．

Ⅰ-1-2　対人コミュニケーションの技法について説明できる（認知）（**表1**）．

Ⅰ-2　良好なコミュニケーション

Ⅰ-2-1　学習者（学生など），他のSP，教員に対して，良好なコミュニケーションができる（技能）．

Ⅰ-2-2　学習者（学生など），他のSP，教員に対して，共感的理解の態度が取れる（態度）．

Ⅰ-3　医療面接におけるコミュニケーション

Ⅰ-3-1　医療面接における患者－医師関係のコミュニケーションの特徴を説明できる（認知）（**表2**）．

Ⅱ. 医学教育におけるSP参加型教育

SPは医学教育に協力するために，SP参加型教育について理解できる．

Ⅱ-1　医学教育における模擬患者と標準模擬患者の違いを理解し，それぞれの役割と意義を説明できる（認知）．

Ⅱ-2　SPとして，能力向上のため必要な知識と技術を習得し，常に自己研鑽に励む態度を持つ（態度）．

Ⅱ-3　学習者（学生など）に対して適切な態度で接することができる（態度）．

Ⅱ-4　教育の目的や対象によってSPの役割が違うことを説明できる（認知）．

Ⅱ-5　当該教育機関の教育指針を理解し，その方針に従って行動できる（態度）．

Ⅱ-6　実習，試験，講習等で得られた事項に関して，守秘することができる（態度）．

Ⅲ. 医学教育における医療面接

1. 医療面接の基本的事項

Ⅲ-1　SPにとって必要な医療面接の基本的な事項について理解できる．

Ⅲ-1-1　医学教育における医療面接の意義を説明できる（認知）．

Ⅲ-1-2　医学教育における医療面接教育の目的について説明できる（認知）．

Ⅲ-1-3　医学教育における医療面接教育のSPの役割を説明できる（認知）．

2. 医療面接シナリオの理解

Ⅲ-2　シナリオを理解できる．

Ⅲ-2-1　シナリオの目的を理解できる（認知）．

Ⅲ-2-2　シナリオの患者背景を理解できる（認知）．

Ⅲ-2-3　シナリオの病状・経過を理解できる（認知）．

Ⅲ-2-4　シナリオに書かれた用語を理解できる（認知）．

3. 役作りと演技

Ⅲ-3　医療面接のシナリオに基づいて，役作りと演技をすることができる．

Ⅲ-3-1　シナリオの内容を記憶し，設定されている背景や気持ちに基づいて役作りができる（技能）.

Ⅲ-3-2　医師役からの質問・説明に対して，シナリオで示されている方向性に則って適切に応答できる（技能）.

Ⅲ-3-3　シナリオに示されている患者を学習目的に沿った現実感のある演技ができる（技能）.

4. フィードバックと評価

Ⅲ-4　医療面接の場面で起きた患者の気持ちの動きを十分に伝えるようなフィードバックができる.

Ⅲ-4-1　医療面接教育におけるフィードバックの目的について説明できる（認知）.

Ⅲ-4-2　医療面接教育におけるフィードバックの教育上の効果を理解できる（認知）.

Ⅲ-4-3　医療面接の場面で起きた出来事と患者の気持ちの動きを記憶できる（技能）.

Ⅲ-4-4　医療面接の場面で起きた出来事と患者の気持ちの動きを適切に言語化できる（技能）.

Ⅲ-4-5　医療面接の場面で起きた出来事と患者の気持ちの動きをSPの視点から教育的にふさわしい形で学習者にフィードバックできる（技能）.

Ⅲ-4-6　評価の目的と方法について理解し，SPの立場から学生の評価ができる（技能）.

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The safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias

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ABSTRACT

Background: Idiopathic interstitial pneumonias (IIPs) are one of the most common complications in patients with lung cancer. In lung cancer patients with IIP, the most serious toxicity is acute exacerbation of IIP caused by anticancer treatment in Japan. However, there has been no consensus and no evidence presented, regarding optimal treatment for advanced lung cancer with IIP.

Patients and methods: Chemotherapy-naïve patients of inoperable stage, or post-operative recurrent non-small cell lung cancer (NSCLC) with IIPs were enrolled. Patients received paclitaxel at a dose of 100 mg/m^2 on Days 1, 8, 15, and carboplatin every 28 days at a target dose of area under the curve (AUC) 5.0 on Day 1.

Results: Between May 2004 and October 2008, 18 patients, including 6 with idiopathic pulmonary fibrosis (IPF), were enrolled and treated for a median of four cycles (range, 1–6). One patient (5.6%; 95% confidence interval (CI), 0–17%) with histologically confirmed IPF had acute exacerbation of IIPs associated with the treatment. The overall response rate was 61% (95% CI, 36–86%). The median progression-free survival, median survival time, and 1-year survival rate were 5.3 months, 10.6 months, and 22%, respectively.

Conclusion: This is the first report indicating that advanced NSCLC patients with IIP may benefit from chemotherapy. Weekly paclitaxel and carboplatin combination chemotherapy was as effective as conventional regimens in advanced NSCLC patients without IIP and was safer than previously reported for NSCLC patients with IIP. The results from this study would support, on ethical grounds, the conduct of a large-scale study to confirm the feasibility of this regimen.

1. Introduction

Idiopathic interstitial pneumonias (IIPs) appear to be associated with lung carcinogenesis. In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) is higher than that in the general population, whose relative risk is reportedly 7–14 [1–5]. Kawasaki et al. [6] reported that IPF was found in 7.5% of surgically resected lung cancer cases. Recently, it has been recognized that IPF is an independent risk factor for lung carcinogenesis [3].

IIPs are usually characterized by slowly progressive respiratory insufficiency. Nevertheless, some IIP patients experience acute exacerbations (AE) generally characterized by suddenly progressive and severe respiratory failure, with new lung opacities and pathological lesions of diffuse alveolar damage (DAD). There are racial differences between Mongolians (including Japanese), and Caucasians in the frequency of AE. Therefore, the concept of AE, which was first proposed in Japan [7,8], has recently come to be recognized globally [9–12]. This clinical condition is lethal in many cases and significantly affects the prognosis of patients with IIP, because there is no established treatment for AE. In lung cancer combined with IIP (LC with IIP), idiopathic or iatrogenic AE frequently occurs following various anticancer treatments. There are only a few retrospective reports of exacerbation of a pre-existing IIP after surgery [13–16], but there are few reports of chemotherapy that are useful in designing a treatment strategy for LC with IIP. At present, there is neither evidence nor consensus around the issue as to whether aggressive treatments such as chemotherapy are appropriate for non-curative NSCLC with IIP.

Abbreviations: IIPs, idiopathic interstitial pneumonias; NSCLC, non-small cell lung carcinoma; AUC, area under the curve; IPF, idiopathic pulmonary fibrosis; CI, confidence interval; SD, standard deviation; AE, acute exacerbation; DAD, diffuse alveolar damage; TXL, paclitaxel; CBDCA, carboplatin; ECOG, Eastern Cooperative Oncology Group; PS, performance status; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; SP-D, surfactant protein D; ORR, objective response rate; PFS, progression free survival; OS, overall survival; MST, median survival time; RECIST, response evaluation criteria in solid tumors; PR, partial response; EGFR, epithelial growth factor receptor.

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The results of our retrospective study of LC with IIP suggested that paclitaxel (TXL) in combination with carboplatin (CBDCA) could be a candidate regimen for treatment of NSCLC patients with IIP [17]. We therefore conducted a prospective study of combined chemotherapy with weekly TXL and CBDCA to assess acceptability, in terms of safety and potential efficacy, in treatment of advanced NSCLC with IIP.

2. Patients and methods

2.1. Study design

Pathologically confirmed, inoperable stage or post-operative recurrent NSCLC patients with IIP who had never received chemotherapy or radiotherapy were eligible for enrollment. They did not include cases with unstable IIPs and acute/subacute IIPs. Patients receiving oxygen inhalation or using immunosuppressive drugs such as steroids were included. Histological types of lung cancer were defined according to the World Health Organization Classification of 1999. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1, and estimated life expectancy > 3 months, measurable lesion, adequate bone marrow, hepatic and renal functions. Written informed consent was obtained from all enrolled patients.

We classified clinical IIP types into two groups: an IPF pattern and a non-IPF pattern. The IPF pattern group consisted of patients with histologically or clinically diagnosed IPF. All other cases were placed in the non-IPF pattern group. Diagnosis of IPF was made in accordance with American Thoracic Society/European Respiratory Society criteria [5] and was previously determined with usual interstitial pneumonia (UIP) by either histological evaluation of open-lung biopsy or transbronchial lung biopsy specimens. In the absence of histological evidence, diagnosis of an IPF pattern was based on evidence from a high-resolution computed tomography (HRCT) scan of the chest and other clinical features. Typical chest CT findings of the IPF pattern were: basal predominant, subpleural reticular abnormality with traction bronchiectasis, honeycomb cysts and no findings of atypical features of IPF, such as peribronchovascular nodules, isolated cysts or consolidation [18–20]. In addition, the presence of other typical clinical features, including bibasilar inspiratory crackles, abnormal findings of pulmonary function tests indicative of restrictive respiratory failure, and increased serum levels of markers of damaged pneumocytes (i.e., lactate dehydrogenase [LDH], C-reactive protein [CRP], KL-6, and surfactant protein D [SP-D]), were investigated. Because we excluded subjects in the acute and subacute phase of IIPs, all patients had either clinical evidence of IPF or fibrotic non-specific interstitial pneumonia (f-NSIP).

Cases were defined as having AE of IIPs if they satisfied all of the following criteria [7,8]: (1) exacerbation of dyspnea within 1 month; (2) newly-developed diffuse pulmonary opacities on chest CT and/or chest X-ray; (3) decrease in arterial oxygen tension (PaO_2) of more than 10 mm Hg under similar conditions; (4) absence of heart failure or infectious lung diseases.

2.2. Study treatment

Patients received TXL 100 mg/m^2 weekly for 3 of 4 weeks and CBDCA (area under the curve (AUC) of 5.0), on Day 1 of each 4-week cycle. Prior to each TXL treatment, patients were given 50 mg diphenhydramine orally, and a histamine H2 receptor blocker intravenously along with 8 mg dexamethasone to prevent anaphylactic shock. Treatment was discontinued when one or more of the following events occurred, disease progression, unacceptable toxicity such as acute exacerbation, patient refusal of further treatment, investigator decision to terminate treatment. No prophylactic granulocyte colony-stimulating factor was planned.

2.3. Statistical considerations

Because this study has been recognized as a pilot study for a large-scale clinical trial, we considered that a large-scale clinical trial can be undertaken when less than two patients present with AE in a cohort of 17 enrolled patients (The probability that more than 25% of the patients would have AE is less than 10%.).

The primary endpoint was the incidence of treatment-related AE. Secondary endpoints were toxicity, the objective response rate (ORR), the median of progression free survival (PFS) and the overall survival (OS). Evaluation was made in compliance with National Cancer Institute common toxicity criteria Version 3.0 for safety, and with response evaluation criteria in solid tumors (RECIST) guidelines [21] for anti-tumor activity. When diagnosis of AE was uncertain, we performed the close inspection necessary for differential diagnoses such as HRCT, evaluation of cardiac function, and bacteriovirological examination. When AE was diagnosed, active treatments such as steroid therapy with intravenous methylprednisolone and/or administration of sivelestat sodium were undertaken. Based on our previous report [17], AE which occurred within 10 weeks after final treatment was considered to be related to chemotherapy.

PFS was measured as a period from the start of this treatment to the identifiable time for progression. Examination values are reported as mean ± standard deviation (SD). Survival time was measured as the period from the start of this treatment until death by all causes. PFS and OS were characterized using the Kaplan–Meier method.

3. Results

3.1. Patients characteristics

Between May 2004 and October 2008, a total of 18 Japanese patients (14 males and 4 females) were enrolled in this study and their characteristics are shown in Table 1. All patients were evaluable for toxicity and survival assessments. The median age at the time of diagnosis of lung cancer was 71 years; 12 patients were current smokers. Six patients were clinically or histologically confirmed cases of IPF. Seven patients had histological confirmation of IIP (6: surgical lung biopsy; 1: transbronchial lung biopsy). No patient had received immunosuppressive agents for IIPs. There were 13 patients with stage IV or post-operative recurrence. Histologically, squamous cell carcinoma and adenocarcinoma were observed in 7 and 6 patients, respectively. The median of 4 cycles of treatment was given (range, 1–7 cycles) and 14 patients received three or more cycles.

Table 2 shows pretreatment demographic parameters of the patients. The mean arterial oxygen tension (PaO_2) was 81.5 mm Hg (range, 69–94) at rest under oxygen free status. No patient routinely required oxygen inhalation. The mean predicted volume capacity in the respiratory function test was 82.0% (range, 35–118). Positive incidence and mean serum levels of KL-6 and surfactant protein D (SP-D) were 67%, 1065 U/ml and 39%, 102.4 ng/ml, respectively.

3.2. Treatment efficacy

Table 3 summarizes the incidence of AE and the anti-tumor effect data. Only one patient with histological IPF developed treatment-related AE (5.6%, 95% CI, 0–17%); this occurred 7 weeks after completion of the 4 cycles of chemotherapy where the efficacy amounted to a partial response (PR), and the patient died from the

Table 1
Patient characteristics.

Number of patients	18
Gender	
Male	14
Female	4
Age (years)	
Median	71
Range	33–81
Smoking status	
Current	12
Former	3
Never	3
IIP pattern	
IPF	6
Non-IPF	12
PS (ECOG)	
0	7
1	11
Stage	
IIIA	2
IIIB	3
IV, recurrent	13
Histology	
Squamous cell	7
Adenocarcinoma	6
Undifferentiated	5

IPF, idiopathic pulmonary fibrosis; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

Table 2
Baseline demographic data.

	Mean	(±SD)
CRP (mg/dL)	2.19	±3.10
LDH (IU/L)	227	±49.6
WBC (mm^3)	8080	±2220
PaO_2 (mm Hg)	81.5	±7.1
KL-6 (U/mL)	1065	±942
Positive rate (%)	67	
SP-D (ng/mL)	108	±70.0
Positive rate (%)	39	
ANA, positive rate (%)	30	
%VC (predicted) (%)	82	±20.0

CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cells; PaO_2, arterial oxygen tension; ANA, antinuclear antibody; SP-D, surfactant protein D; %VC, percent vital capacity; SD, standard deviation.

Table 3
Incidence of acute exacerbation and objective response to treatment.

Number of patients (%)	18
Acute exacerbation	
Treatment-related	1
(to death)	1
2nd line treatment-related	3
(to death)	1
Treatment unrelated	1
(to death)	1
Objective response	
CR + PR	11
SD	4
PD	2
NE	1
Overall response rate (%)	61

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

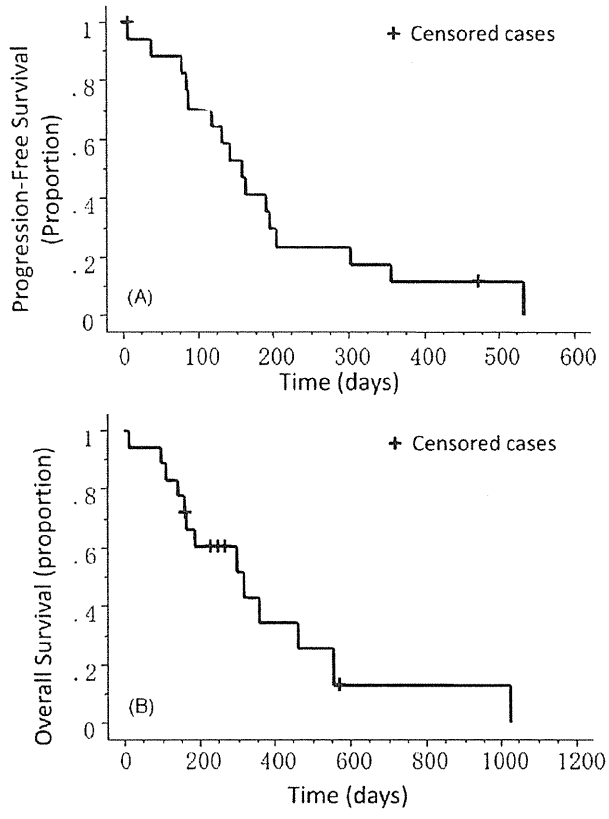

Fig. 1. (A) Progression-free survival (PFS) and (B) overall survival (OS). Vertical bars indicate censored cases at the data cutoff point. The median PFS, median survival time (MST), and 1-year survival rate were 5.3 months, 10.6 months, and 22%, respectively.

event after 8 weeks. Three patients developed AE related to second-line chemotherapy (2: docetaxel alone; 1: gefitinib). Moreover, AE unrelated to treatment was observed in one patient, who developed AE 8 months after last administration of TXL. Two of 5 patients with AE had histologically confirmed UIP by open-lung biopsy. The remaining 3 patients were non-IPF pattern including one patient with histologically confirmed NSIP.

The overall response rate (ORR) was 61% (95% CI, 36–86%). Stable and progressive disease were observed in 4 patients and 2 patients, respectively. One patient dropped out due to hypersensitivity before first evaluation of the response and so could not be evaluated.

Survival analysis performed in May 2009 showed that 16 patients had died. The median PFS was 5.3 months (Fig. 1A). The median survival time (MST) was 10.6 months, and 1-year survival rate was 22% (Fig. 1B).

3.3. Toxicities

Treatment-related adverse events other than AE are summarized in Table 4. The most common hematological grade 3 and 4 adverse event was neutropenia (33%), although febrile neutropenia was observed in only one patient. Non-hematological adverse events were generally mild and the most common such event was peripheral neuropathy. All 4 patients with neuropathy were grade 2. One cerebral infarction (grade 3) and one hypersensitivity (grade 3) were also observed, both of which were considered to have been possibly related to the treatment. The improvement in condition of 2 patients was good, and second-line treatment was performed.

Table 4
Treatment-related adverse events excluding acute exacerbation.

Toxicity	Grade 2	Grade 3	Grade 4	Grade 3 or 4	(%)
Hematological toxicity					
Leukocytopenia		5	0	5	28
Neutropenia		4	2	6	33
Fibrile neutropenia		1	0	1	6
Anemia		0	0	0	0
Thrombocytopenia		0	0	0	0
Non-hematological toxicity:					
Peripheral neuropathy	4	0	0	0	0
Myalgia	1	0	0	0	0
Nausea	2	0	0	0	0
Cerebral infarction		1	0	1	6
Hypersensitivity		1	0	1	6

4. Discussion

Optimal chemotherapy for treatment of advanced LC with IIP still remains controversial, because there have been few reports focusing on AE of IIPs related to chemotherapy for lung cancer. This is the first prospective study to analyze the safety and efficacy of a specific regimen for LC with IIP. In this pilot study of weekly TXL combined with CBDCA for advanced NSCLC with IIP, we observed an incidence of treatment-related AE of 5.6%. In the case of chemotherapy, the incidence of treatment-related AE previously reported ranged from 8.7% to 21% in Japan. However, AE is now increasingly being recognized as a common clinical event.

Attention is now being paid to the induction of AE of IIPs by anticancer agents, following reports in Japan of ILD developing after treatment with the epithelial growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib. In 3166 Japanese patients with advanced/recurrent NSCLC enrolled in a cohort and nested case–control study, gefitinib-induced interstitial lung disease was manifested in 3.98%. This is about 13-fold higher compared to that in the U.S.A., where the incidence is 0.3% [FDA Approval Letter for Iressa]. More interestingly, that study demonstrated that a predisposing background of pre-existing IIPs was an independent risk factor for developing AE, regardless of gefitinib therapy or other chemotherapies (odds ratio, 4.8–5.6) [26].

Recently, it has become a well-known phenomenon that IIP patients without lung cancer develop AE in the normal course of the disease. Kim et al. retrospectively reported that 1-year frequency was 8.5% after diagnosis [27]. Kubo et al. reported a high incidence of AE (64%) in the control group of a randomized study on the role of anticoagulants [28]. In another prospective randomized study on the role of pirfenidone, Azuma and colleagues found a 14% incidence in 35 untreated patients during a 9-month follow-up period [29]. In this study, AE unrelated to anticancer treatment was observed in 1 patient and in 3 patients related to second-line chemotherapy. This suggests that this chemotherapy regimen can be employed safely in patients with IIP.

Localization of active oxygen and a growth factor, inflammatory cytokine or vascularization factor, to lung tissue plays an important role in inducing inflammation [30]. It seems that these factors induced by anticancer treatment may have been one cause of AE. However, a useful predictive risk factor for AE or drug-induced ILD has not yet been identified. In our previous report, KL-6, SP-D, PaO_2 and %VC, which are considered to be markers of progression of IIPs, were not predictive of developing AE. There was no statistically significant difference in clinical background or values for pretreatment demographics between those who did and did not experience AE [17]. The existence of focal usual interstitial pneumonia, which was undetectable by conventional chest CT, but confirmed in a biopsy specimen, was reported to be closely related to AE after lung resection for lung cancer in Japan. This suggests that disease severity and progression of IIPs are not always correlated with the risk of AE.

Currently, TXL combined with CBDCA administered every 3 weeks is most widely use for advanced NSCLC as the established standard regimen. A weekly TXL schedule has been reported have good safety and efficacy for high-risk patients such as the elderly and those previously treated [32–34]. We observed an ORR of 61% and median PFS of 5.3 months, which was comparable to the results of the randomized phase III trial in Japanese patients without IIPs (ORR, 32.4%; median PFS, 4.5 months) [35]. However, the MST (10.6 months) and 1-year survival rate (22%) in this study would be regarded as unsatisfactory for patients without ILD. Nonetheless, the results were as good as those based on a weekly regimen for elderly patients [33,34]. Because of the difference between comparatively good PFS and unsatisfactory OS, we considered that only 6 of 16 patients, excluding one patient for treatment-related death and one progression-free patient, received second-line chemotherapy.

The chemotherapy regime described above was selected since no recommended regimen previously existed. To reduce levels of toxicity and complications, especially severe neutropenia causing the different infectious diseases, and over-hydration causing lung congestion, we selected chemotherapy regimens based on weekly schedules of TXL and CBDCA. The incidence of myelosuppression in this study could thereby be decreased compared to that previously reported, and non-hematological toxicities were mostly mild to moderate and manageable.

In conclusion, the combination of weekly TXL and a 4-weekly schedule of CBDCA used in the present study was effective for advanced NSCLC patients with IIP and appeared to be more safe than suggested by previous reports. Previously, these patients have usually been treated with best supportive care alone because no standard treatment had been established. This is the first report indicating that chemotherapy for LC with IIP may be beneficial.

To further confirm the feasibility of weekly TXL combined with CBDCA for advanced NSCLC with IIP, we are now carrying out a more large-scale clinical trial and detailed evaluation.

Conflict of interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgement

Author contributions: Drs. Minegishi, Kudoh and Gemma devised the conception of the study and designed the methods. Dr. Minegishi raised funding wrote manuscript drafts, was responsible for data management and statistical analyses. Drs. Minegishi, Sudoh, Kuribayashi, Mizutani, and Seike were responsible for implementing the study. Drs. Azuma and Yoshimura assisted in the trial design, and reviewed the manuscript. Dr. Gemma provided final approval of the version to be published.

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The Feasibility Study of Carboplatin Plus Etoposide for Advanced Small Cell Lung Cancer with Idiopathic Interstitial Pneumonias

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Background: Idiopathic interstitial pneumonias (IIPs) are among the most common complications in patients with lung cancer. In such patients with cancer, the most serious expression of toxicity in Japan is acute exacerbation of IIPs caused by anticancer treatment. Nevertheless, there has been no consensus and no evidence presented, regarding optimal treatment for advanced lung cancer with IIP.

Patients and Methods: Chemotherapy-naive patients with advanced small cell lung cancer (SCLC) with IIP who were ineligible for curative radiotherapy were enrolled. Patients received carboplatin every 21 days at a dose of area under the curve 6.0 on day 1 and etoposide at a dose of 100 mg/m^2 on days 1 to 3.

Results: Between July 2002 and October 2008, 17 patients with SCLC with IIP, including 14 men, eight of whom were diagnosed with idiopathic pulmonary fibrosis, were enrolled and treated for a mean of 3.5 cycles of carboplatin plus etoposide. One patient (5.9%; 95% confidence interval, 0–18.4%) with clinically confirmed idiopathic pulmonary fibrosis had acute exacerbation of IIPs associated with the treatment. The overall response rate was 88.2%. The median progression-free survival, median survival time, and 1-year survival rate were 5.5 months, 8.7 months, and 29.4%, respectively.

Conclusion: This is the first report indicating that patients with advanced SCLC with IIPs may benefit from chemotherapy. Patients with advanced SCLC with IIP treated with etoposide and carboplatin combination chemotherapy gain benefits, with safety equivalent to that seen in patients without IIP. The results from this study would support, on ethical grounds, the conduct of a large-scale study to evaluate this regimen.

Key Words: Idiopathic interstitial pneumonias, Idiopathic pulmonary fibrosis, Acute exacerbation, Small-cell lung cancer, Chemotherapy.

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Small cell lung cancer (SCLC) is characterized by a rapid doubling time, a propensity for early dissemination, significant sensitivity to chemotherapy and radiotherapy, and accounts for approximately 15 to 20% of all cases of lung cancer diagnosed. The majority of these patients have extensive stage disease at the time of diagnosis. The standard treatment for patients with extensive stage SCLC is systemic chemotherapy with a combination of cisplatin and etoposide, a regimen that yields a median survival of approximately 9 months and a 2-year survival of less than 10%.[1–3] Nevertheless, elderly or poor performance status (PS) patients often have poor tolerance for a cisplatin-containing regimen. Therefore, carboplatin is widely used as an alternative.[4,5]

Idiopathic interstitial pneumonias (IIPs) seem to be associated with lung carcinogenesis. In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) is higher than that in the general population, whose relative risk is reportedly 7 to 14.[6–10] Kawasaki et al.[11] reported that IPF was found in 7.5% of surgically resected lung cancer cases. Recently, it has been recognized that IPF is an independent risk factor for lung carcinogenesis.[8]

IIPs are usually characterized by slowly progressive respiratory insufficiency. Nevertheless, some patients with IIP experience acute exacerbations (AEs) generally characterized by suddenly progressive and severe respiratory failure, with new lung opacities and pathological lesions of diffuse alveolar damage. There are racial differences between Mongolians (including Japanese) and whites in the frequency of AE. Therefore, the concept of AE, which was first proposed in Japan,[12,13] has recently come to be recognized globally.[14–17] This clinical condition is lethal in many cases and significantly affects the prognosis of patients with IIP, because there is no established treatment for AE. In patients with lung cancer combined with IIP (lung cancer [LC] with IIP), idiopathic or iatrogenic AE frequently occurs after various anticancer treatments. There are some retrospective reports of exacerbation of a preexisting IIP after surgery,[18–21] but there are only a few reports of chemotherapy that are useful in designing a treatment strategy for LC with IIP. We previously indicated that combination chemotherapy with carboplatin and paclitaxel had significant antitumor efficacy and permissible safety in treatment of non-small cell lung

cancer (NSCLC) with IIP. In a limited sample size, this pilot trial showed that the response rate was as good as that of standard chemotherapy for NSCLC without IIP, and the incidence (5.6%) of AE of IIPs was lower than that in previous reports.[22]

The results of our retrospective study of LC with IIP suggested that combined chemotherapy with carboplatin and etoposide (CE) could be a candidate regimen for treatment of patients with SCLC with IIP.[23] We, therefore, conducted a prospective study of CE to assess its acceptability, in terms of safety and efficacy, in treatment of advanced SCLC with IIP.

PATIENTS AND METHODS

Study Design

Pathologically confirmed chemotherapy-naive patients with SCLC with IIPs, for whom curative radiotherapy was impossible, were eligible for enrollment. These did not include cases with unstable IIPs and acute/subacute IIPs. Patients receiving oxygen inhalation or using immunosuppressive drugs such as steroids were eligible. Histological types of lung cancer were defined according to the World Health Organization Classification of 1999. Additional eligibility criteria included Eastern Cooperative Oncology Group PS 0 to 2 and estimated life expectancy more than 3 months, measurable lesion, adequate bone marrow, hepatic, and renal functions. Written informed consent was obtained from all enrolled patients. We obtained an approval in relationship to institutional review boards in our institution.

We classified clinical IIP types into two groups: an IPF pattern and a non-IPF pattern. The IPF pattern group consisted of patients with histologically or clinically diagnosed IPF. All other cases were placed in the non-IPF pattern group. Diagnosis of IPF was made in accordance with American Thoracic Society/European Respiratory Society criteria[10] in patients previously diagnosed with usual interstitial pneumonia by either histological evaluation of open-lung biopsy or transbronchial lung biopsy specimens. In the absence of histological evidence, diagnosis of an IPF pattern was based on evidence from a high-resolution computed tomography (HRCT) scan of the chest and other clinical features. Typical chest CT findings for the IPF pattern were basal predominant, subpleural reticular abnormality with traction bronchiectasis, honeycomb cysts, and no findings of atypical features such as peribronchovascular nodules, isolated cysts, or consolidation.[24–26] In addition, the presence of other typical clinical features, including bibasilar inspiratory crackles, abnormal findings of pulmonary function tests indicative of restrictive respiratory failure, and increased serum levels of markers of damaged pneumocytes (i.e., lactate dehydrogenase [LDH], C-reactive protein [CRP], KL-6, and surfactant protein D [SP-D]) were investigated. Because we excluded subjects in the acute and subacute phase of IIPs, all patients had either clinical evidence of IPF or fibrotic nonspecific interstitial pneumonia.

Cases were defined as having AE of IIPs if they satisfied all the following criteria[12,13]: (1) exacerbation of dyspnea within 1 month; (2) newly developed diffuse pulmonary opacities on chest CT and/or chest x-ray; (3) decrease in arterial oxygen tension (Pao_2) of more than 10 mmHg under similar conditions; and (4) absence of heart failure or infectious lung diseases.

Study Treatment

Patients received carboplatin (area under the curve of 6.0) intravenously (IV) over 60 minutes on day 1, which was followed by etoposide 100 mg/m^2 IV over 60 minutes on days 1 to 3, every 3 weeks. No prophylactic granulocyte colony-stimulating factor (G-CSF) was planned. All patients received standard supportive care, as appropriate. Treatment was discontinued when one or more of the following events occurred: disease progression, unacceptable toxicity such as AE, patient refusal of further treatment, and investigator decision to terminate treatment. Patients were monitored for the development of AE for a minimum of 10 weeks after last administration of etoposide.

Statistical Considerations

Because this study has been recognized as a pilot study for a large-scale clinical trial, we considered that a large-scale clinical trial could be undertaken when less than two patients present with AE in a cohort of 17 enrolled patients (the probability that >25% of the patients would have AE is <10%).

The primary end point was the incidence of treatment-related AE. Secondary end points were toxicity, the objective response rate (ORR), the median progression-free survival (PFS), and the overall survival (OS). Evaluation was made in compliance with National Cancer Institute common toxicity criteria Version 3.0 for safety and with RECIST guidelines[27] for antitumor activity. When diagnosis of AE was uncertain, we performed the close inspection necessary for differential diagnoses such as HRCT, evaluation of cardiac function, and bacteriovirological examination. When AE was diagnosed, active treatments such as steroid therapy with IV administration of methylprednisolone and/or administration of sivelestat sodium were undertaken. Based on our previous report,[23] AE occurring within 10 weeks after final treatment was considered to be related to chemotherapy.

Examination values are reported as mean ± standard deviation. PFS was measured as the period from the start of this treatment to the identifiable time for progression. Survival time was measured as the period from the start of this treatment until death by all causes. PFS and OS were characterized using the Kaplan-Meier method. Odds ratios (ORs) and 95% confidence intervals (CIs) to assess the relative risk of AE were calculated by logistic regression analysis. Resulting p values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

Between July 2002 and October 2008, a total of 17 Japanese patients (14 men and 3 women) were enrolled in this study, and their characteristics are listed in Table 1. All patients were evaluable for toxicity and survival assessments. The median age at the time of diagnosis of lung cancer was 69 years; all patients were current or former smokers. Eight

TABLE 1. Patient Characteristics

No. of patients	17	
Gender		
Male	14	82%
Female	3	18%
Age (yr)		
Median	69	
Range	53–80	
PS (ECOG)		
0	4	23%
1	10	59%
2	3	18%
Stage		
IIIA	5	29%
IIIB	3	18%
IV	9	53%
IIPs pattern		
IPF	8	47%
Non-IPF	9	53%

PS, performance status; ECOG, Eastern Cooperative Oncology Group; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis.

TABLE 2. Baseline Demographic Data

	Mean	±SD
CRP		
mg/dl	1.96	±3.29
LDH		
IU/L	412	±228
WBC		
mm^3	7540	±2020
Pao_2		
Torr	77.8	±11.8
KL-6		
U/ml	956	±563
Positive (>500)	86 (%)	
SP-D		
ng/ml	111.9	±75.3
Positive (>110)	33 (%)	
ANA		
Positive (>40×)	57 (%)	
%VC		
Predicted	91.4	±16.9

CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cells; Pao_2, arterial oxygen tension; ANA, antinuclear antibody; SP-D, surfactant protein D; %VC, percent vital capacity; SD, standard deviation.

TABLE 3. Incidence of Acute Exacerbation and Objective Response to Treatment

No. of patients	17
Acute exacerbation	
Treatment related	1
To death	1
Second-line treatment related	2
To death	1
Treatment unrelated	2
To death	2
Objective response	
CR + PR	15
SD	1
PD	1
Overall response rate	88.2%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

patients were clinically confirmed cases of IPF, and nine were determined to be non-IPF pattern. There were no patients in whom histological confirmation of interstitial pneumonias was obtained. There were two patients who were diagnosed as collagen-vascular disease after the study treatment (one rheumatoid arthritis and one systemic sclerosis). One patient had received immunosuppressive agents for IIPs. This patient had a history of AE of IPF and was given 20 mg prednisolone orally. The patient received the five cycles of chemotherapy safely. Two patients routinely required oxygen inhalation for IIPs. There were nine patients with stage IV and three patients with stage IIIB. There were five patients with stage IIIA in whom chemoradiotherapy was avoided.

Table 2 presents pretreatment demographic parameters of patients. The mean serum levels of CRP and LDH were 1.96 mg/dl and 412 IU/L respectively. The mean Pao_2 was 77.8 mmHg (range, 58–99) at rest under oxygen-free status. The mean predicted vital capacity (%VC) in the respiratory function test was 91.4% (range, 69–108). Positive incidence and mean serum levels of KL-6 and SP-D were 86%, 956 U/ml and 33%, 111.9 ng/ml, respectively.

Treatment Efficacy

Table 3 summarizes the incidence of AE and the antitumor effect data. Only one patient with clinical IPF developed treatment-related AE (5.9%, 95% CI, 0–18.4%); this occurred 9 weeks after completion of the five cycles of chemotherapy where the efficacy amounted to a partial response, and the patient died of the event after 4 weeks. The survival time of this patient after registration was 38 weeks. Two patients developed AE related to second-line chemotherapy, and one patient died due to AE. Moreover, AE unrelated to treatment was observed in two patients; these patients developed AE 8 months and over 3 months after last administration of etoposide, respectively. Four of five patients with AE had clinical IPF. The incidence and mortality from AE in the total follow-up period were 29.4% and 23.5%, respectively.

The ORR was 88.2% (95% CI, 71–100%), comprising one complete response and 14 partial responses. Stable and progressive diseases were observed in one patient each. Survival analysis performed in April 2010 showed that 14 patients had died. The median follow-up period was 9 months; we could not confirm the final outcome of one patient. The median PFS was 5.5 months (Figure 1*A*), which compared well with that of 4.8 months in the Japan Clinical Oncology Group (JCOG) 9511 trial[1] with cisplatin + etoposide for SCLC without IIP. In addition, the median survival time (MST) was 8.7 months, and 1-year survival rate was

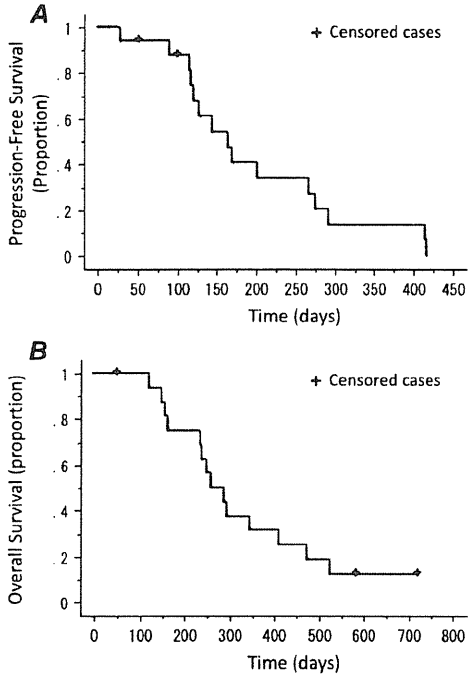

FIGURE 1. *A*, Progression-free survival (PFS) and (*B*) overall survival (OS). Vertical bars indicate censored cases at the data cutoff point. The median PFS, median survival time (MST), and 1-year survival rate were 5.3 months, 10.6 months, and 22%, respectively.

TABLE 4. Treatment-Related Adverse Events Excluding Acute Exacerbation

Toxicity	Grade 2	Grade 3	Grade 4	Grade 3–4	Percentage
Hematological					
Leukocytopenia		11	3	14	82.4
Neutropenia		3	12	15	88.2
Febrile neutropenia		2	0	2	11.8
Anemia	4	4	1	5	29.4
Thrombocytopenia	1	4	1	5	29.4
Nonhematological					
Nausea	4	1	0	1	5.9
Vomiting	1	0	0	0	0
Diarrhea	1	1	0	1	5.9
Congestive heart failure			1	1	5.9

Grade, National Cancer Institute Common Toxicity Criteria version 3.0.

29% (Figure 1*B*), compared with MST and 1-year survival rate of JCOG 9511 of 9.4 months and 37.7%, respectively.

Toxicities

Treatment-related adverse events other than AE are summarized in Table 4. The most common hematological grades 3 and 4 adverse event was neutropenia (88.2%), although febrile neutropenia was observed in two patients. Nonhematological adverse events were generally mild, the most common of which were nausea and vomiting. Only one patient with nausea was grade 3. One grade 3 congestive heart failure patient was also observed, which was considered to have been possibly due to the treatment. The improvement in condition of patients was good, and second-line treatment was performed. A mean of 3.5 cycles of treatment was given (range, 1–6 cycles), and 14 patients received three or more cycles.

TABLE 5. Patient Characteristics of SCLC and NSCLC with IIP

No. of patients	35	
Gender		
Male	28	80%
Female	7	20%
Age (yr)		
Median	69	
Range	33–81	
Performance status		
0	11	31%
1	21	60%
2	3	9%
Smoking status		
Current	25	71%
Former	7	20%
Never	3	9%
IIPs pattern		
IPF	14	40%
Non-IPF	21	60%
Acute exacerbation		
First line	2	5.7%
Second line	5	14.3%
Unrelated	3	8.6%
Total	10	28.6%

SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis.

The Risk Factor of AE

In selecting patients, it can be recommended that those cases at high risk of AE of IIPs be excluded with a view to improvement of treatment safety. To evaluate the risk factor of AE, we conducted an analysis that integrated this study with that of NSCLC with IIP, which we reported previously.[22] Integrated patient characteristics and AE status are listed in Table 5. A total number of 35 patients were included in this integrated analysis. There were 10 patients in total with AE for the following reasons: first-line chemotherapy related, two cases; second-line chemotherapy related, five cases; and treatment unrelated, three cases. Thirty-two smokers (current and former, 91%) and three never smokers (9%) were observed. IPF and non-IPF patterns were observed in 14 (40%) and 21 (60%) patients, respectively.

Univariate analyses of various risk factors, such as clinical features and laboratory parameter, for AE in patients who had LC with IIP are presented in Table 6. Regarding clinical features, the ORs were 2.8 for men and 3.5 for elderly patients (more than median age), but neither was significant. The risk of AE in those with the IPF pattern was not