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CQ 3 インドレント（くすぶり型，予後不良因子を持たない慢性型）ATLの標準治療は無治療経過観察か

推奨グレード
カテゴリー2B

インドレントATLに対する化学療法は生存期間の延長にはつながらず，無治療経過観察が推奨される。

解　説

九州および沖縄の40施設におけるくすぶり型および慢性型ATL 337例を対象とした後方視的解析では[1]，その生存期間中央値（MST）はそれぞれ5.2年と3.6年であった。そのサブグループ解析では，くすぶり型での無治療群と抗がん剤投与群との間で全生存期間（OS）に差はなかった。一方，慢性型では無治療群の方が抗がん剤投与群よりも有意に生存期間が長かった（MST 7.4年 vs 2.0年）。また，1988～1997年に九州の多施設でくすぶり型ATLと診断された26例のMSTは7.3年（観察期間中央値6.5年）であった[2]。また，単施設での後方視的研究報告によると，1974～2003年にくすぶり型（25例），慢性型（予後不良因子を持つ慢性型37例，予後不良因子を持たない慢性型26例，不明2例）と診断され，増悪するまで無治療経過観察が行われた計90例では，観察期間中央値が4.1年の時点で12人が10年以上生存していた。しかし，2年，5年，10年，15年生存割合はそれぞれ約60%，47%，23%，13%と長期予後は不良であった[3]。MSTと無増悪MSTはそれぞれ4.1年と3.3年であり，くすぶり型と慢性型の生存曲線がいずれもプラトーに到達せず下降したことから，増悪後のMSTは約1年と推定され，MSTは長く長期生存例が一定の割合で存在するものの，増悪後の予後は不良であることが示唆される。

以上のようにインドレントATLの長期予後は決して良好ではない。しかし，有効な治療法がまだ見出されていないため，急性転化まで無治療で経過観察することが，わが国では現在コンセンサスとして定着している。

くすぶり型で皮膚病変のみを持つ症例の局所治療は，皮膚悪性腫瘍診療ガイドライン[4]の参照が推奨される。

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CQ 4 再発・難治アグレッシブATLに対する治療法は何が勧められるか

推奨グレード
カテゴリー2B

現時点で同種造血幹細胞移植が生存に寄与する唯一の救援療法である。モガムリズマブの有用性については現在評価中である。

解　説

アグレッシブATLに対してはこれまでさまざまな化学療法が試みられてきたが，一旦治療効果が得られてもその持続期間は短く，その後は急速な経過を辿ることが多い。そのため臨床試験の遂行は困難で，単施設での少数例の報告がほとんどである。わが国における modified EPOCH 療法（ETP, DXR, CPA, VCR, PSL）[1]，ペントスタチン[2]，ソブゾキサン[3]，塩酸イリノテカンとシスプラチン併用[4]などの小規模な第Ⅰ・Ⅱ相試験の結果が報告されている。いずれも奏効割合は30～40%であったが，効果持続期間は1～6ヵ月であった。

ケモカイン受容体のCCR4はATLの90%以上で発現しており，予後不良因子でもある。ヒト化抗CCR4抗体（モガムリズマブ）の第Ⅰ相試験では再発難治のアグレッシブATL 13名中4名に治療反応がみられ[5]，さらには至適投与量の単剤での第Ⅱ相試験で13/26名（50%，うち8名はCR）に奏効したことが報告された[6]。2012年5月よりモガムリズマブは再発・難治性ATLに対して承認された。現在，初発のアグレッシブATLを対象としたモガムリズマブとVCAP-AMP-VECP療法［VCAP（VCR, CPA, DXR, PSL），AMP（DXR, MCNU, PSL），VECP（VDS, ETP, CBDCA, PSL）］との併用療法のランダム化第Ⅱ相比較試験が進行中であり，今後の評価が必要である。

CQ2にあるように，同種造血幹細胞移植（allogeneic hematopoietic stem cell transplantation：allo-HSCT）は化学療法後の再発・難治アグレッシブATLの一部に長期生存をもたらすことが複数の報告で示されている。

局所再発の場合，症状緩和を目的とした局所放射線療法を行ってもよい[7]。

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CQ 5 ATLに対するインターフェロンαとジドブジンの併用療法は有用か

推奨グレード
カテゴリー3

ATLに対するインターフェロンα/ジドブジン療法は，一般診療としては推奨されない。

解　説

ATLはCHOP療法などのリンパ腫に対する標準治療では難治であり，HTLV-1が関与することから，欧米ではインターフェロンα（IFNα）とジドブジン（AZT）の併用療法が検討され，1995年には2つの小規模な臨床試験でアグレッシブATLに対する有望な奏効割合が報じられた[1)2)]。しかし，初発例に限るとその奏効割合と生存期間中央値（MST）は当時のJCOG-LSGによる化学療法より下回っていたこともあって，日本でこの治療法は本格的に検討されなかった[1)~3)]。2010年に，欧州と北中南米での後方視的併合解析において，リンパ腫型よりも白血化している急性型，慢性型，くすぶり型で本治療法が有用であったと報告された[4)]。これを受けてNCCNガイドラインでは，リンパ腫型以外のATLに対してIFNα/AZT療法を推奨している（NCCNガイドライン：カテゴリー2A）。またこの報告では，IFNα/AZT療法群での治療成績は白血化しているこれらの3病型で化学療法群を上回っていた一方，急性型ATLに対する化学療法の治療成績は，日本での化学療法の成績を下回っていた。一方，慢性型とくすぶり型では，症例数は少ないものの観察期間中央値5年で全例が生存しており，皮膚病変の改善にも有用と報告された[4)]。本併用療法は，長期にわたる治療が必要であり，倦怠感などの全身症状，造血障害など多様な有害事象を認めるものの，化学療法や同種造血幹細胞移植（allogeneic hematopoietic stem cell transplantation：allo-HSCT）に比べて毒性は低いと報告されている。

以上よりIFNα/AZT療法は，確かにATLに対して有望な治療法であるが，これまでの海外での小規模な臨床的検討と後方視的解析によるエビデンスが十分でないことから，一般診療では推奨されない。なお，IFNα，AZTともにATLでは国内適応外である。現在わが国で，インドレントATLに対するIFNα/AZT療法と無治療経過観察との比較試験が計画されている。

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MEETING REPORT

Meeting report on the possible proposal of an extranodal primary cutaneous variant in the lymphoma type of adult T-cell leukemia-lymphoma

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ABSTRACT

Based on the advances in research on the clinicopathophysiology of adult T-cell leukemia-lymphoma (ATL), Japanese researchers collected and evaluated cases of smoldering ATL exhibiting primary cutaneous manifestation but showing poor prognosis. Macroscopic findings of skin eruptions were categorized into the patch, plaque, multipapular, nodulotumoral, erythrodermic and purpuric types, as previously reported. Pathological findings were divided into low or high grade based on epidermotropism, tumor cell size and perivascular infiltration. Eight eligible cases were evaluated among 14 collected cases. Macroscopic findings were nodulotumoral in six cases, a subcutaneous tumor in one case and plaque in one case, and the number and size were heterogeneous in each case. Pathological findings of all eight cases were T-cell lymphoma, high-grade type (pleomorphic, medium or large size), with prominent perivascular infiltration and scant epidermotropism. To diagnose such cases as the "lymphoma type of ATL, extranodal primary cutaneous variant", it is essential to examine each case carefully, including cutaneous lesions at onset, lymph nodes and other organ involvement using computed tomography (CT) and/or positron emission tomography/CT, as well as the percentage of abnormal lymphocytes in peripheral blood. Based on the results of an ongoing nationwide survey on ATL, ATL with cutaneous lesions will be analyzed to investigate the incidence and prognosis of the so-called "lymphoma type of ATL, extranodal primary cutaneous variant".

Key words: **adult T-cell leukemia/lymphoma, extranodal primary cutaneous variant, lymphoma type adult T-cell leukemia/lymphoma, smoldering adult T-cell leukemia/lymphoma.**

PURPOSE OF THE MEETING

On the basis of the modes of initial presentation and natural history of patients with adult T-cell leukemia/lymphoma (ATL), the four clinical subtypes of acute, lymphoma, chronic and smoldering have been recognized. Diagnostic criteria for the clinical subtypes were proposed[1] and significant prognostic factors were determined in 1991.[2] Since then, patients with ATL were stratified into two groups, aggressive ones consisting of acute, lymphoma and unfavorable chronic types, and indolent ones consisting of favorable chronic and smoldering types, in which the chronic type was further divided into favorable

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and unfavorable according to significant prognostic factors. This stratification was useful for the selection of treatment, in which most patients with aggressive forms were treated with systemic chemotherapy, while those with indolent forms underwent watchful waiting or local therapy only.

In the clinical subtype classification, however, the lymphoma type did not include extranodal variants because of the rarity of such cases at that time. Since then, variants of extranodal lymphoma type such as primary cutaneous ATL and primary gastrointestinal ATL have been reported. The extranodal primary cutaneous variant included in smoldering type made it particularly difficult for physicians to choose the initial treatment.[3–6] Furthermore, the extranodal primary gastrointestinal variant included in the acute type was reported to respond to treatment and be associated with long-term survival. On the contrary, the localized lymphoma type, which was rare in the initial survey in Japan, was reported to consist of approximately 10% of acute and lymphoma types of ATL, and was associated with relatively favorable prognosis after chemotherapy in a recent nationwide survey in Japan.[7]

Based on the advances in research on the clinicopathophysiology of ATL as described above, Japanese researchers, focusing on ATL, joined by the support of a grant (H23-gan rinsho-ippan-022), collected and evaluated cases such as of the localized lymphoma type and extranodal variants originating from several organs to reconsider the subclassification for the appropriate selection of treatment.

This research group, consisting of Japanese hematologists, dermatologists, pathologists, epidemiologists and oncovirologists, aimed at collecting cases as follows: smoldering type with primary cutaneous manifestation resulting in poor prognosis, acute type with the manifestation of an extranodal variant of primary gastrointestinal or nasopharyngeal type, and localized lymphoma type, reviewing clinicopathological findings and proposing the consensus report.

This report summarizes the discussion of the first meeting on this project, focusing on the extranodal primary cutaneous variant.

ELIGIBILITY CRITERIA OF PATIENTS FOR THE EVALUATION

Eligibility criteria included smoldering ATL with only cutaneous lesions confirmed by histopathology, and with survival after diagnosis of less than 1 year as a rule but less than 3 years being allowed. Each dermatologist/hematologist picked up the cases, and filled out the case report forms with macro-photographs and histological specimens of cutaneous lesions. We categorized the macroscopic findings of skin eruptions into the patch, plaque, multipapular, nodulotumoral, erythrodermic and purpuric types, as previously reported.[6] When multiple types of skin eruption exist in a patient, the most severe type should be described if a consensus on the hierarchy of severity in the types exists: patch and plaque were considered the lowest and second lowest severity, respectively, and nodulotumoral was most severe. There was no consensus on multipapular, erythrodermic and purpuric types, but multipapular and purpuric types were considered intermediate between nodulotumoral and plaque, and should be described separately. Erythrodermic type should still be carefully evaluated. Subcutaneous tumors were specified but included as the nodulotumoral type.

Pathological findings were divided into low or high grade based on epidermotropism, the cell size and perivascular infiltration.[3]

RESULTS

Fourteen cases were evaluated, but six of them were deemed ineligible because of the period from the onset of cutaneous lesions to the diagnosis of ATL being more than 4 months in five cases and concurrent lymph node lesions at onset not indicating the smoldering but acute type in one case. Case reports were provided by Dr Y. Sawada (University of Occupational and Environmental Health, Fukuoka), Dr Y. Uchida (Kagoshima University, Kagoshima), Dr T. Johno (Kumamoto University, Kumamoto), Dr M. Takenaka (Nagasaki University, Nagasaki), Dr K. Uchimaru (Tokyo University, Tokyo) and Dr K. Tobinai (National Cancer Center Hospital, Tokyo).

All of the eight eligible cases were diagnosed as smoldering ATL. Macroscopic findings were nodulotumoral in six cases, a subcutaneous tumor in one case and plaque in one case, and the number and size were heterogeneous in each case. Pathological findings of all eight cases were consistent with T-cell lymphoma, high-grade type (pleomorphic, medium or large size), with prominent perivascular infiltration and scant epidermotropism. Median times from the diagnosis to acute crisis, and onset of the cutaneous lesion to acute crisis, were 6 and 7 months, respectively (data not shown).

DISCUSSION (PROBLEMS AND TO-DO LIST)

Accurate evaluation is essential at onset: cutaneous lesion at onset, lymph nodes and other organ involvement using computed tomography (CT) and/or positron emission tomography (PET)/CT, as well as the percentage of abnormal lymphocytes in peripheral blood (PB).

The clinical course of each lesion including cutaneous lesions should be evaluated with respect to the timing of diagnosis. As for the "extranodal primary cutaneous variant", further case evaluation is essential, including those with a relatively favorable prognosis.

As for the pathological diagnosis of cutaneous lesions, the biopsy site including macroscopic findings should be described. It is possible that specimens were biopsied at sites with a poor prognostic hierarchy in this case series.

In general, pathological findings of cutaneous lesion of ATL appear to be epidermotropic and non-epidermotropic. All of the cases in this meeting were high-grade peripheral T-cell lymphoma (PTCL)-like, and no case was low-grade cutaneous T-cell lymphoma-like because cases with a poor prognosis were collected.

Seven out of eight eligible cases were the "extranodal primary cutaneous variant", consisting of six cases of nodulotu-

moral and one of plaque macroscopically, and all seven were high-grade PTCL microscopically. The remaining one was described as a "primary subcutaneous tumor". There was a comment against the "primary subcutaneous tumor" type included in the "primary cutaneous variant".

To diagnose such cases as the "lymphoma type of ATL, extranodal primary cutaneous variant", it is essential to examine each case carefully, including cutaneous lesions at onset, lymph nodes and other organ involvement using CT and/or PET/CT, as well as the percentage of abnormal lymphocytes in PB (Appendix 1).

The application of clinical staging based on the extension of cutaneous lesions requires further investigation.

Some ATL patients with multipapular type cutaneous lesions were reported to show a rapidly progressive clinical course.[6] Such cases should also be collected and analyzed.

FUTURE PLAN

More cases should be collected and investigated.

Based on the results of an ongoing nationwide survey on ATL, ATL with cutaneous lesions will be analyzed to investigate the incidence and prognosis of the so-called the "lymphoma type of ATL, extranodal primary cutaneous variant".

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APPENDIX I

For the diagnostic criteria of the lymphoma type of the extranodal primary cutaneous variant, no definite appearance of abnormal cells in PB (≤1%) is essential.

Evaluation of abnormal lymphocytes by flow cytometry as well as based on the morphology is warranted to calculate the cells as a real number. However, such criteria are quite different from the original criteria for the definition of ATL and clinical subtype classification of ATL. Therefore, such a proposal requires careful analyses and evaluation. Discussion on this issue is currently limited in this meeting.

For ATL, quantitative evaluation of cutaneous lesions such as using the modified Severity Weighted Assessment Tool should be investigated; however, it is not easily applicable.

Macroscopic findings of cutaneous lesions are a significant prognostic factor in ATL. However, the combination of other parameters, for example, tumor markers such as lactate dehydrogenase and soluble IL-2 receptor, needs to be investigated.

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Prognostic Index for Acute- and Lymphoma-Type Adult T-Cell Leukemia/Lymphoma

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ABSTRACT

Purpose
The prognosis of acute- and lymphoma-type adult T-cell leukemia/lymphoma (ATL) is poor, but there is marked diversity in survival outcomes. The aim of this study was to develop a prognostic index (PI) for acute- and lymphoma-type ATL (ATL-PI).

Patients and Methods
In a retrospective review, data from 807 patients newly diagnosed with acute- and lymphoma-type ATL between January 2000 and May 2009 were evaluated. We randomly divided subjects into training (n = 404) and validation (n = 403) samples, and developed a PI using a multivariable fractional polynomial model.

Results
Median overall survival time (MST) for the 807 patients was 7.7 months. The Ann Arbor stage (I and II *v* III and IV), performance status (0 to 1 *v* 2 to 4), and three continuous variables (age, serum albumin, and soluble interleukin-2 receptor [sIL-2R]) were identified as independent prognostic factors in the training sample. Using these variables, a prognostic model was devised to identify different levels of risk. In the validation sample, MSTs were 3.6, 7.3, and 16.2 months for patients at high, intermediate, and low risk, respectively ($P < .001$; $\chi^2 = 89.7$, 2 *df*; log-rank test). We also simplified the original ATL-PI according to dichotomizing age at 70 years, serum albumin at 3.5 g/dL, and sIL-2R at 20,000 U/mL and developed an easily calculable PI with prognostic discrimination power ($P < .001$; $\chi^2 = 74.2$, 2 *df*; log-rank test).

Conclusion
The ATL-PI is a promising new tool for identifying patients with acute- and lymphoma-type ATL at different risks.

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INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by human T-cell lymphotropic virus type I (HTLV-1).[1,2] HTLV-1 is endemic to the southwestern region of Japan, Caribbean basin, Central and South America, and western Africa. The cumulative incidence of ATL is estimated to be approximately 2.5% to 5% among HTLV-1 carriers.[3,4] Patients with ATL present with characteristic clinical features such as increased abnormal lymphocytes with cerebriform or flower-like nuclei (flower cells) in the peripheral blood, hypercalcemia, skin lesions, generalized lymphadenopathy, and hepatosplenomegaly accompanied by opportunistic infections.[1,5] A previous report by the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG) identified five prognostic factors for ATL, including advanced performance status (PS), high lactic dehydrogenase (LDH), age of 40 years or older, total involved lesions, and hypercalcemia, on the basis of an analysis of 854 patients with newly diagnosed ATL registered between 1983 and 1987.[6] The JCOG-LSG then proposed four clinical subtypes: acute, lymphoma, chronic, and smoldering types. This system is known as Shimoyama classification and is based on prognostic factors and clinical features of the disease.[7] This classification is now widely used for determining therapeutic strategy. Generally, the prognosis of acute- and lymphoma-type ATL is poor, whereas that of the chronic and smoldering types is better. More than two decades have passed since the pivotal reports by JCOG-LSG, and ATL management has improved over this period. Recently, an International Consensus Meeting recommended treatment using chemotherapies

such as a vincristine, cyclophosphamide, doxorubicin, and prednisolone (VCAP) plus doxorubicin, ranimustine, and prednisolone (AMP) plus vindesine, etoposide, carboplatin, and prednisolone (VECP), which is a sequential combination chemotherapy consisting of VCAP, AMP, and VECP[8,9] with or without subsequent allogeneic hematopoietic cell transplantation (HCT) for acute- and lymphoma-type ATL, and a combination of interferon alfa and zidovudine (IFN/AZT) for acute-type ATL outside of clinical trials.[10]

However, there are diverse clinical courses and survival outcomes among patients with acute- and lymphoma-type ATL. Therefore, it is necessary to establish a prognostic index (PI) for a risk-adapted approach and to improve the quality of clinical trials. To determine prognosis in patients with acute- and lymphoma-type ATL, we elucidated prognostic factors by performing a nationwide survey of patients diagnosed during the past decade and developed a PI.

PATIENTS AND METHODS

Patients

We conducted a retrospective survey of patients with ATL diagnosed between January 1, 2000, and May 31, 2009, in Japan. The inclusion criterion for this investigation was a diagnosis of acute- and lymphoma-type ATL based on Shimoyama classification. Patients who had undergone allogeneic HCT were excluded from this analysis because there is an undetermined impact on survival using this novel intervention. All clinical data as well as the validity of diagnosis of ATL were centrally reviewed by two expert hematologists.

Clinical Data

We collected information regarding sex, age, institutional based–clinical subtype, WBC counts, neutrophil counts, lymphoid cell counts, abnormal lymphoid cell counts, hemoglobin, platelet counts, serum total protein, serum albumin, blood urea nitrogen (BUN), LDH, soluble interleukin-2 receptor (sIL-2R), presence of hypercalcemia, C-reactive protein, maximum tumor size, "B" symptoms, PS by Eastern Cooperative Oncology Group (ECOG), Ann Arbor stage, and number of lesions of involved lymph nodes, as well as the sites and number of involved extranodal lesions. We defined leukemic stage IV disease as the presence of more than 1% of abnormal lymphocytes in peripheral blood according to the definition for diagnosing acute- and lymphoma-type ATL in Shimoyama classification.[7] Overall survival (OS) was calculated from the time of diagnosis to the date of death by any cause or to the last follow-up date.

Approval of the study procedure was obtained from the ethics committee and institutional review board of the coordinating center (Fukuoka University) and at each participating center on the basis of their institutional policies.

Statistical Analysis

The data set was randomly split into either a training sample for developing a PI or a validation sample for evaluating the obtained PI. Continuous variables were not categorized a priori because categorizing a predictor would result in an inevitable loss of information.[11] We applied parametric models based on two-degree fractional polynomial (FP) functions to retain relevant variables continuous.[12] For each continuous variable X, one or two terms of the form X^p were fitted with powers, p, which were chosen from (-2, -1, -0.5, 0, 0.5, 1, 2, and 3). The association of each variable with OS was evaluated using a univariable FP model, and variables showing a P value of less than .05 were considered candidate predictors. Then, the multivariable FP (MFP) procedure using backward elimination was performed. The backward elimination was based on closed testing,[12] and a P value of less than .05 was used for variable selection. A continuous PI from the final MFP model was categorized into three risk groups, with two optimal cutoff points in the continuous PI found by maximizing the log-rank statistics according to the minimal P value approach.

An explorative simplification of our continuous PI was developed, dichotomizing all the predictors a priori according to their standard cutoff points. Concordance between three risk groups from the simplified PI and those from the original PI was measured using weighted κ.

Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC) with %mfp8 macro[13] and MATLAB (Mathworks, Natick, MA). All P values were reported as two-sided.

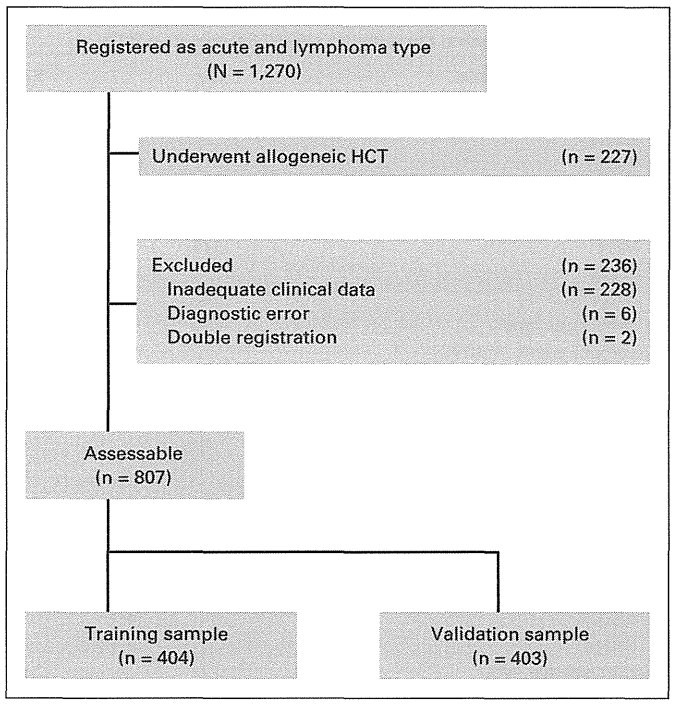

Fig 1. CONSORT flowchart of patients: 1,270 patients diagnosed with acute- and lymphoma-type adult T-cell leukemia/lymphoma were registered. Of these patients, 227 patients were excluded because they had undergone allogeneic hematopoietic cell transplantation (HCT). Two hundred thirty-six patients were excluded for the following reasons: 228 for inadequate clinical data at diagnosis because they had at least one missing value of covariates in Table 1, six for diagnostic error, and two for double registration. The remaining 807 patients were analyzed and randomly divided into training (n = 404) and validation (n = 403) samples.

RESULTS

Patient Characteristics

Data from 1,270 patients with acute- and lymphoma-type ATL were submitted from 81 institutions across Japan (Fig 1). A total of 227 patients had undergone allogeneic HCT and were excluded. Of the remaining 1,043 patients, 236 patients were excluded for the following reasons: 228 for inadequate clinical data at diagnosis because they had at least one missing value of covariates in Table 1, six for diagnostic error, and two for double registration. Thus 807 patients were analyzed for the development of the PI. Baseline characteristics are shown in Table 1. Deaths were observed in 641 patients (79%), and the median overall survival time (MST) was 7.7 months (95% CI, 7.0 to 8.7 months). The most common cause of death was progressive disease (81.3%). Death from infection without disease progression was 13.4%.

The number of patients who received initial treatment was 765 (95%), whereas 37 (4.6%) did not receive any treatment, and five were uncertain. Of the 765 patients who had received initial treatment, 755

Table 1. Baseline Characteristics of All Patients (n = 807)

Characteristic	No.	%
Age, years		
Median	67	
Range	35-91	
Sex		
Female	383	47
Male	424	53
Subtype		
Acute type	564	70
Lymphoma type	243	30
Neutrophil count, × 10^9/L		
Median	5.2	
Range	0.16-37	
Hemoglobin level, g/dL		
Median	13	
Range	7.4-18.0	
Platelet count, × 10^9/L		
Median	206	
Range	8-885	
Serum total protein, g/dL		
Median	6.6	
Range	3.2-8.9	
Serum albumin, g/dL		
Median	3.6	
Range	1.8-5.8	
BUN, mg/dL		
Median	16	
Range	3.6-118.3	
LDH, IU/L		
Median	621	
Range	127-13,813	
LDH > 2 × ULN	457	57
Soluble IL-2R, U/mL		
Median	22,800	
Range	303-683,000	
Hypercalcemia present	279	35
Increased CRP present	576	65
Ann Arbor stage		
I-II	77	10
III-IV	730	90
ECOG PS		
0-1	396	49
2-4	411	51
B symptoms present	252	31
No. of lymph node lesions		
Median	3	
Range	0-8	
No. of extranodal sites		
Median	1	
Range	0-7	
No. of total involved lesions		
Median	4	
Range	0-13	
Bone marrow involvement present	252	31
Liver involvement present	96	12
Spleen involvement present	138	17
Pleural effusion present	97	12
Ascites present	63	8

NOTE. The soluble IL-2R level by pg/mL can be converted to U/mL using the formula: value (pg/mL) × 0.113.

Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; IL-2R, interleukin-2 receptor; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 2. Results of Variable Selection by the MFP Model in the Training Sample (n = 404)

Variable	HR	95% CI	*P*
Stage			
I-II	1.00		
III-IV	1.91	1.25 to 2.92	.003
ECOG PS			
0-1	1.00		
2-4	1.42	1.13 to 1.80	.003
Age, years (continuous)	1.02	1.01 to 1.03	.007
Serum albumin, g/dL (continuous)	0.70	0.57 to 0.87	.001
Log_{10}(sIL-2R), U/mL (continuous)	1.45	1.19 to 1.76	< .001

Abbreviations: ECOG PS; Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MFP, multivariable fractional polynomial; sIL-2R, soluble interleukin-2 receptor.

had chemotherapy and 10 patients had undergone lesion-directed treatment (Appendix Fig A1, online only). No patient received IFN/AZT, which is considered a standard treatment for acute-type ATL in the world,[10,14] because this combination of agents has not been approved for ATL in Japan.

Development of the PI

We randomly selected 404 patients (50% of the 807 patients) as a training sample and developed a PI based on this set. First, in univariate analysis with the two-degree univariable FP model, all variables except sex showed *P* values less than .05 (likelihood ratio test). We then performed backward elimination using the MFP model. Variables that remained independently significant included Ann Arbor stage (I or II *v* III or IV), ECOG PS (0 to 1 *v* 2 to 4), and the three continuous variables of age, serum albumin, and sIL-2R. The MFP model yielded a significant nonlinear function for sIL-2R (log transformation), whereas the other four variables fitted linearly, thus allowing an expression of a final multivariate model in terms of the usual Cox regression model. The estimated hazard ratios and their 95% CIs in the final multivariate model in the training sample are shown in Table 2. A linear risk function based on Cox regression coefficients (ie, the log of hazard ratios), which hereafter we call ATL-PI, was as follows: ATL-PI = 0.65 (if stage = III or IV) + 0.35 (if ECOG PS > 1) + 0.016 × age (years) − 0.36 × albumin (g/dL) + 0.37 × $\log_{10}$ (sIL-2R [U/mL]).

The median of the ATL-PI in the training sample was 2.13 (range, 0.30 to 3.48), 10% of values were less than 1.31, and 90% of values were less than 2.86. Potential cutoff points between 1.30 and 2.90 were evaluated, and the value of 2.6 showed the best discrimination on the basis of the log-rank test (1 *df*) and was defined as the high-risk group for 91 patients (23%, ATL-PI ≥ 2.6). To define the low-risk group, the value of 1.6 was chosen as the best discriminator using the log-rank test (2 *df*), and 76 patients were classified as low risk (19%, ATL-PI < 1.6). The distribution of ATL-PI was similar in the validation sample (n = 403) with high-, intermediate-, and low-risk groups of 99 (25%), 232 (56%), and 72 (18%) patients, respectively, using the designated cutoff points. The three risk groups according to the ATL-PI were effectively prognostic in the validation sample, as shown in Figure 2 ($P < .001$; $\chi^2 = 89.7$, 2 *df*; log-rank test). MSTs were 3.6 (95% CI, 2.4 to 4.6), 7.3 (95% CI, 6.4 to 8.5), and 16.2 (95% CI, 14.5 to 24.7) months for patients at high, intermediate, and low risk, respectively, and OS rates