合いを重ね，出産直後は母乳を与えることに決めた。出産後3か月で夫に協力してもらいながら断乳した。第2子(次男)出産後も同様に短期授乳を実施した。

今回は女児出産予定で，将来彼女が母親となる時に自分のように悩ませたくないため，これまで以上に感染させたくないという気持ちが強い。しかし母乳は与えたいので，今回は凍結解凍母乳にしたい。

悩みぬいた様子の妊婦さん

由美さんが外来へいらっしゃった時，疲れたような硬い表情でした。肩で息をする様子や大きなおなかが目立ちました。ご主人の運転で1時間以上かけて来院されたとのこと。遠方から妊娠35週目の妊婦さんを迎える側としては，彼女の体調や心理状態が不安でしたが，彼女がいったん話し出すと次々と言葉があふれ，今まで溜まっていたものが一気に流れ出た，という感じでした。話し続ける彼女の隣に座っているご主人が，うんうんとうなずいていらっしゃるのも印象的でした。

話し続けた由美さんからは，「悩み抜いた」様子がよく伝わってきました。そのことを彼女へお話しすると，強ばっていた表情が少し穏やかになりました。また，今回は凍結解凍母乳を希望されていることから，確認の意味でその方法や短期母乳との相違点を問うと，彼女はすでに栄養方法に関して産科施設で相談されていて，要領を得ている様子でした。

自分の体についての不安は口にしない

私は，由美さんが出産間近でありながら，わざわざこの外来に来られた意味について考えさせられました。「子どもに感染させたくない」「子どもに自分と同じように悩ませたくない」という言葉に表われる気持ちもつらいものですが，「キャリアであるがゆえにこれほど悩まねばならない」というやり場のない思いもまたつらく悲しいことと思います。彼女が妊娠のたびに悩み抜いている姿は痛々しく，もし自分が発症してしまったら幼い子どもはどうなってしまうのか，さらに，万が一子どもが感染していたらという不安，恐れや焦りも伝わってきます。自分の体がウイルスに脅かされる不安や恐怖ももちろんあると思いますが，彼女たちはそのようなことは言葉に表わしません。そこにまたつらさを感じます。

一通り話し終えると，由美さんは久しぶりの出産ということで「また1から出直しです」とかわいらしくにっこりと微笑み，和やかな雰囲気で面接を終えました。私は話してくださったことへのお礼と出産の無事を祈ること，かかりつけの産科施設の助産師さんにも改めて相談されることを彼女にお勧めして別れました。

ケース2 美樹さん(仮名，50代)

20年前，長男を妊娠した時の検査でHTLV-1キャリアとわかった。産科医師より，「母乳で感染する病気のウイルスだから母乳はあげないほうがよい」と言われた。ショックだった。ウイルス感染の原因は夫の出身地が関係していると思っていた。一方で，夫の妹が母乳を与えていたことを不思議に思った。

美樹さんは感染の理由について自分が思っていることを夫に話さなかったが，ウイルスが母乳から子どもに感染する可能性と，母乳をあげるか迷っていることを夫に伝えた。すると夫は「(母乳を)あげて感染するなら，あげないほうがいい。仕方がない」と言ったため，断乳することに決めた。

その後出産で帰省した際に受診した産科施設では「母乳をあげてもよかったのに」と言われた。前の病院とはまったく逆のことを言われて驚いたが，夫との取り決めどおり断乳した。産後，夫は彼女が母乳をあげないことに対する周囲の疑念や非難から彼女をひたすら守ってくれた。

第2子，第3子を出産した際も断乳した。その時受診した産院では「母乳をあげてはいけない」と言われた。2人目を出産した後乳腺炎になり，あまりの痛みに耐えきれず涙したり，薬疹が出たこともあった。3人目を出産した後，子どもが泣くと母乳が出てきたが，泣いてもあげられないという経験をした。また，検査を勧められて子どもと小児科に受診すると，採血のために検査室に連れて行かれた子どもの泣きわめく声が聞こえた。その声を聞きなが

ら自分を責めた。1番下の子は検査を受けなかった。

子どもの成長にともないウイルスのことを忘れることが多くなったが，子育てで悩んだ時，母乳をあげていないことが影響したのではないかと思う時があった。また，自分が体調を崩して病院受診した際，自分がHTLV-1キャリアであることを医師へ伝えると，医師の表情が急に険しくなったことがあった。医師からは定期的な検査を勧められたが，その時の医師の印象のせいで逆に病院から遠ざかってしまった。そして現在，当院の専門外来の存在を知り，ここなら受診してみたいという気になったため，来院した。

人生が揺さぶられてきた体験

ケース2の美樹さんは明るくさっぱりした感じの方でした。現時点でHTLV-1関連の病気の有無を検査するためと，カウンセリング目的で受診された女性でした。

事例の概略をみると，キャリアであることで彼女の人生が揺さぶられてきた様子がよく伝わってくると思います。揺さぶられるたびに自分を責めたり，恐怖心を抱いたり，感染に関しては戸惑いながらも夫と良好な関係を築きながら生きている姿がみえます。また彼女は自身の傷ついた体験から，ある内科医師の表情に敏感に反応されていたのではないかと思われます。私は彼女の爽やかな笑顔を前に，よくここまで乗り越えられてきたなと，感動さえ覚えました。

カウンセリングは，キャリアの方が背負い続けている荷物を，わずかな時間でもカウンセラーに預けてもらって休んでいただくような場だと思います。個人差はあってもキャリアの方は，どこか恐れのような気持ちをもち続けていらっしゃるようです。こういったこころの緊張を解す意味でも，定期検診とともに継続的なカウンセリングを受けることの必要性を感じます。

「子どもの声を聞いて自分を責めた」という経験は，キャリアの方たちにとって最もつらいことの1つだと思います。ケース1の由美さんの場合にもありましたが，自分自身が脅かされる恐怖感を表に出すことなく子への自責の念をずっともち続けているのが，キャリアの母親たちに共通してみられる気持ちだと思われます。

病気についての誤解

美樹さんがウィルスに関して理解していたことのなかに，少し違和感を覚えるような事柄がありました。それは彼女の思い込みからくる誤解でしたが，相談の場において，相談者が思い込んでいることに間違いがあれば，正しい情報を提供することは大切です。しかし，その時「間違い」という言葉を強調すれば，その方は自分の人格が否定されたように受け取られることがありますので，注意が必要です。

私は，美樹さんが妊娠中に気持ちに混乱をきたしながらも，キャリアであることを受容していったのではないかと考えました。当院の専門外来を受診し医師からウイルスの説明を受けた美樹さんは，「自分が思っていたことは間違いだったんだ」と思ったそうです。このように，あっさりと見方を変えられる場合もあります。私はこのお話を聞いて，改めて，妊娠中に自身がキャリアとわかった方の気持ちが，複雑で閉ざされたものになりがちであることを教えられたように思いました。

「大丈夫」と言われても

美樹さんは「自分はいいのです。子どもが感染しなかったら」とおっしゃいました。しかし，HAMの患者さんたちが自身の病が難病であると知って涙を浮かべるのを見る時，私はキャリアの母親たちのことを思い出します。また，あるATLの男性が「僕の母親は悪くないよ」とおっしゃったことも忘れられません。キャリアの母親が「大丈夫」と言葉に出しても，時には彼女たちの気持ちの揺れに同調したり，彼女たちの気持ちが折れないように支えてあげるような在り方が援助者として大切だと思われます。

また，由美さんも美樹さんも夫の協力のもとで育児を乗り切っています。キャリアである告知は，最初はご本人だけにされるようになっていますが，キャリアが告知された後で，誰とどの時点

でつながっていくかという視点をもつことも，キャリア支援で重要なことと考えます。

小さい数をもってしまった大勢の人へ

美樹さんとのお話のなかで「感染率などの数値はあるが，自分のようなキャリアに関しては0か1かが問題であって，10か100かは問題ではない」と教えていただきました。私たちはつい，数字の大きさや量に物事の価値を置いてしまいがちですが，「少数である」という事実に心を傷めている方が大勢存在することを忘れてはならないと思います。一方で，日本全国にHTLV-1キャリアが少なくとも108万人存在するといわれている事実は静観できることではありません。

人生の何かのきっかけで不安や恐怖を感じるのがHTLV-1キャリアのこころです。そして，キャリアの母親たちは自分自身がウイルスに脅かされる恐怖を語らず，子どもの健康に対する心配や，キャリアになってしまったという自責の念を抱き続けています。

キャリアは無症状であり，彼女たちのつらさは目に見えにくいものです。だからこそ，キャリアの気持ちを言葉にしていきながらキャリアの人生を支えるようなかかわりが必要だと考えます。❶

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Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A)

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Summary

This study evaluated the clinical features of 276 patients with aggressive adult T-cell leukaemia-lymphoma (ATL) in 3 Japan Clinical Oncology Group (JCOG) trials. We assessed the long-term survivors who survived >5 years and constructed a prognostic index (PI), named the JCOG-PI, based on covariates obtained by Cox regression analysis. The median survival time (MST) of the entire cohort was 11 months. In 37 patients who survived >5 years, no disease-related deaths in 10 patients with lymphoma-type were observed in contrast to the 10 ATL-related deaths in other types. In multivariate analysis of 193 patients, the JCOG-PI based on corrected calcium levels and performance status identified moderate and high risk groups with an MST of 14 and 8 months respectively (hazard ratio, 1·926). The JCOG-PI was reproducible in an external validation. Patients with lymphoma-type who survived >5 years might have been cured. The JCOG-PI is valuable for identifying patients with extremely poor prognosis and will be useful for the design of future trials combining new drugs or investigational treatment strategies.

Keywords: adult T-cell leukaemia-lymphoma, Japan Clinical Oncology Group trials, long-term survivors, prognostic index.

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Adult T-cell leukaemia-lymphoma (ATL) is a distinct peripheral T-lymphocytic malignancy associated with human T-cell lymphotropic virus type I (HTLV-1) (Uchiyama *et al*, 1977; Poiesz *et al*, 1980; Hinuma *et al*, 1981; Miyoshi *et al*, 1981; Yoshida *et al*, 1982). Classification of clinical subtypes into acute, lymphoma, chronic and smouldering was proposed based on prognostic factors, clinical features and the natural history of the disease (Shimoyama, 1991). Patients with aggressive ATL (i.e., acute, lymphoma and unfavourable chronic types) have frequently been treated as a subtype of aggressive non-Hodgkin lymphoma (NHL), whereas those with indolent ATL (i.e., favourable chronic and smouldering types) have been managed as a subtype of chronic lymphoid leukaemia (Shimoyama, 1994; Tobinai & Watanabe, 2004). Aggressive ATL typically has a very poor prognosis compared with aggressive B-cell lymphomas, such as diffuse large B-cell lymphoma and peripheral T-cell lymphoma excluding ATL (The International Non-Hodgkin's Lymphoma Prognostic Factor Project's, 1993; Shimoyama, 1994; Gallamini *et al*, 2004; Watanabe *et al*, 2010). In the 1980's, patients with aggressive ATL were reported to have a median survival time (MST) of approximately 8 months, with a 2-year survival rate of <5% because of the multidrug-resistant phenotype of their malignant tumour cells, rapid proliferation of the tumour cells, a large tumour burden with multi-organ failure, hypercalcaemia, and/or frequent opportunistic infections (Lymphoma Study Group, 1991; Shimoyama, 1991, 1994; Tobinai & Watanabe, 2004).

The Japan Clinical Oncology Group (JCOG)-Lymphoma Study Group (LSG) has conducted consecutive clinical trials to improve the survival of patients with ATL. Earlier trials (JCOG7801, JCOG8101, and JCOG8701) revealed poor prognosis of ATL compared with other aggressive NHLs (Shimoyama *et al*, 1988; Tobinai *et al*, 1994). Furthermore, the disappointing results with conventional chemotherapies in the 1980s and the proposal for a subtype classification of ATL led us to conduct clinical trials with new agents that exclusively targeted aggressive ATL. The first phase II trial, JCOG9109 (1991–1993), evaluated combination chemotherapy with deoxycoformycin, an inhibitor of adenosine deaminase, which had been effective as a single agent against relapsed or refractory ATL (Tobinai *et al*, 1992). However, the results were disappointing with an MST of 7 months, similar to the findings of previous JCOG-LSG trials (Tsukasaki *et al*, 2003). The next phase II trial, JCOG9303 (1994–1996), evaluated the chemotherapy regimen VCAP-AMP-VECP (LSG15) against aggressive ATL. This dose-intensified multi-agent chemotherapy consisted of vincristine, cyclophosphamide, doxorubicin (DXR) and prednisone (PSL) for VCAP, DXR, ranimustine and PSL for AMP, and vindesine, etopside, carboplatin and PSL for VECP, supported by granulocyte colony-stimulating factor and intrathecal (IT) prophylaxis with methotrexate (MTX) and PSL. This phase II trial showed promising results, with complete remission (CR) and overall response rates of 36% and 81%, respectively, and an MST of 13 months at the expense of haematological and other toxicities (Yamada *et al*, 2001). Based on these results, we proceeded to the phase III trial JCOG9801 (1998–2003), which compared a modified VCAP-AMP-VECP regimen (shortened from 7 to 6 courses), to which cytarabine was added to the IT prophylaxis, *versus* CHOP (cyclophosphamide, DXR, vincristine and PSL)-14 supported by granulocyte

colony-stimulating factor and IT prophylaxis identical to the former regimen. The CR and 3-year overall survival (OS) were higher in the modified VCAP-AMP-VECP arm than in the CHOP-14 arm (40% vs. 25% and 24% vs. 13% respectively), suggesting that the former is a more effective regimen at the expense of greater toxicity for patients with newly diagnosed aggressive ATL (Tsukasaki *et al*, 2007).

Through these 3 JCOG trials for patients with aggressive ATL, the 5-year OS was improved, from 5% in the 1980's to 15% in the 1990s. To characterize the long-term survivors of aggressive ATL and to develop a new prognostic index (PI) for the disease, we performed a combined analysis (JCOG0902A) of all the patients enrolled in the 3 JCOG trials.

Methods

Study population

A total of 276 patients who were registered in the 3 JCOG trials described above were enrolled in this study (Yamada *et al*, 2001; Tsukasaki *et al*, 2003, 2007). Some patients did not receive anti-viral therapy using interferon-alpha and zidovudine because these drugs for ATL was not covered by the National Health Insurance in Japan. The eligibility criteria for the 3 JCOG trials were detailed in previous reports (Yamada *et al*, 2001; Tsukasaki *et al*, 2003, 2007). Briefly, patients were eligible to participate if they had aggressive ATL (i.e., acute, lymphoma, or unfavourable chronic type) with no prior chemotherapy, were aged 15–69 years and had preserved organ functions, no proven central nervous system (CNS) involvement and a performance status (PS) of 0–3 or 4 due to hypercalcaemia caused by ATL. The diagnosis of ATL was made based on seropositivity for HTLV-1 antibody and histologically and/or cytologically proven peripheral T-cell malignancy. Monoclonal integration of HTLV-1 provirus was analysed in 104 of 276 patients studied. Among these 104 patients, integration was detected in 100 patients and not detected in four patients.

The PI for the JCOG trials, which we refer to as the JCOG-PI, was constructed from the data of patients who participated in these trials (training set) and was then applied to an external validation set. The external validation set consisted of 136 patients who had not participated in prior JCOG studies but had received anthracycline-containing regimens as initial chemotherapy at three sites (Nagasaki University Hospital, Nagasaki Medical Centre, and Sasebo City General Hospital) under the remit of the JCOG-LSG. These patients were a subset of those from a previous retrospective study (Katsuya *et al*, 2012) and their OS and corrected calcium levels were reviewed.

Data and analysis sets

The endpoint of this study was OS, defined as the duration between registration to each JCOG trial and death from any cause or censored at the last follow up in living patients. For the validation data set, we substituted the date of treatment initiation for the date of registration.

Candidate covariates were sex, age, Eastern Cooperative Oncology Group (ECOG) PS, B symptoms, clinical stage, liver involvement, lactate dehydrogenase, blood urea nitrogen (BUN), corrected calcium levels, serum total protein, serum albumin, white blood cell count, total (normal and abnormal) lymphocyte count, neutrophil count and platelet count. We excluded the treatment regimen from the covariates because our aim was to create an index that could stratify the patients' prognosis and be applicable to future clinical trials evaluating various promising regimens. Cut-off values were determined clinically by dividing the continuous biological and laboratory test variables into no more than three categories. The data of 193 patients with a complete set of candidate covariates were used for the training set (Fig 1).

The protocol of this study was reviewed and approved by the JCOG Protocol Review Committee.

Statistical analysis

Patients who survived >5 years were categorized according to ATL subtype (acute, lymphoma or unfavourable chronic types). In addition, to evaluate the ATL-related death events for each subtype, a disease-specific mortality curve was estimated, for only those patients who survived >2 years, by means of a competing risks framework (Kalbfleisch & Prentice, 2002). The proportion of patients who survived >5 and >10 years was calculated to evaluate the association between long-term survival and CR (including CR unconfirmed) for initial treatment. The proportion of cases with

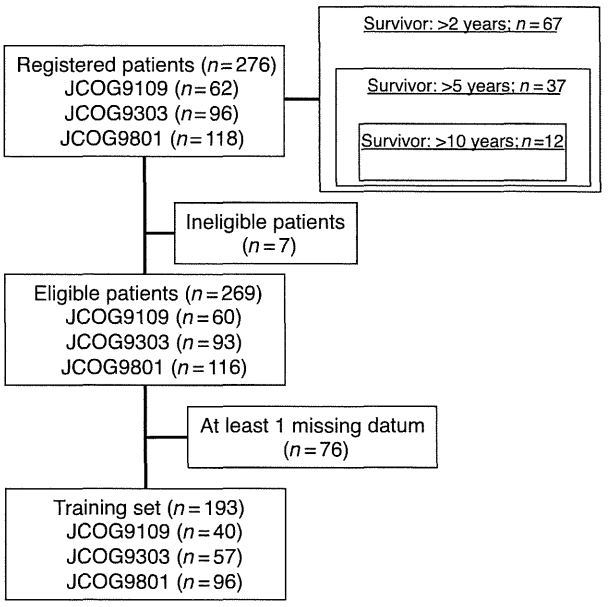

Fig 1. Patient disposition of the training set.

CNS involvement was compared among the JCOG trial regimens in an exploratory evaluation of the efficacy of prophylactic IT treatment. The prophylactic IT treatments against CNS involvement were: none in JCOG9109, MTX and PSL in JCOG9303, and MTX, cytarabine and PSL in both regimens in JCOG9801. Confidence intervals (CIs) for all the above proportions were computed using the Clopper–Pearson method (Clopper & Pearson, 1934).

Analyses for the development and validation of the JCOG-PI were performed according to a pre-specified analysis plan. The JCOG-PI consisted of risk groups that were developed using Cox's proportional hazards model. Before constructing the JCOG-PI, covariates with several definitions were selected for those with the smallest Akaike's Information Criteria (Akaike, 1973) on univariate analysis. Next, we verified the correlations between covariates to avoid multi-colinearity. Stepwise Cox regression analysis was then performed to identify unfavourable prognostic factors for constructing the JCOG-PI. The entry criterion was $P < 0{\cdot}20$ and the removal criterion was $P > 0{\cdot}15$.

The maximum number of risk group strata was set at three, based on the opinions of JCOG-LSG members who commented that too many strata were impractical for evaluating risk. The risk group was divided with patients equally distributed. The log-rank test was used to assess the discrepancy between the risk groups and the Kaplan–Meier method was applied to estimate OS.

All statistical analysis was performed using SAS Release 9·1 (SAS Institute, Inc, Cary, NC, USA). All reported P values are two-sided and $P < 0{\cdot}05$ was considered statistically significant.

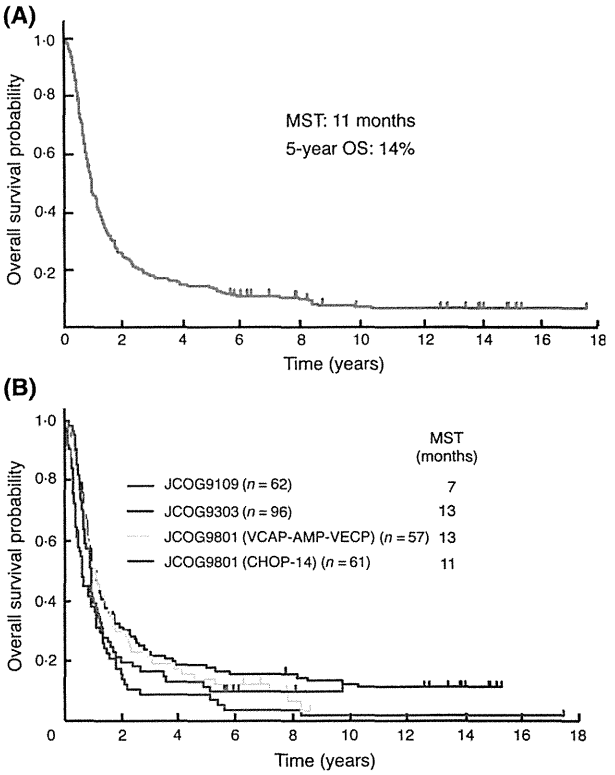

Fig 2. Overall survival (OS) of all registered patients in 3 Japan Clinical Oncology Group (JCOG) trials and according to treatment regimens. (A) OS of all 276 registered patients. Median survival time (MST) and the 5-year OS were 11 months and 14%, respectively.(B) OS according to different treatment regimens. MST was 7 months in JCOG9109, 13 months in JCOG9303, 13 months in VCAP-AMP-VECP of JCOG9801 and 11 months in CHOP-14 of JCOG9801.

Results

Patient characteristics

A total of 276 patients were registered in the 3 trials (JCOG9109, $n = 62$; JCOG9303, $n = 96$; and JCOG9801, $n = 118$) from 58 institutions in Japan. The MST and the 5-year OS of all patients were 11 months and 14% respectively (Fig 2A). The OS of each treatment regimen during the long follow up reconfirmed the findings of each original report (Fig 2B) (Yamada *et al*, 2001; Tsukasaki *et al*, 2003, 2007). Clinical characteristics are shown in Table I.

Long-term survivors according to subtype and initial response

The disease-specific mortality curve of patients who survived >2 years according to subtype is presented in Fig 3. Among the 37 patients (acute, $n = 22$; lymphoma, $n = 8$; unfavourable chronic, $n = 7$) who survived >5 years, there were no ATL-related deaths in lymphoma type, which was in contrast to the 10 ATL-related deaths in the acute and unfavourable chronic types after 5 years.

Of the 276 patients, 88 (32%) achieved CR with initial treatment. Of these 88 patients, 24 (27%) patients had survived >5 years and 11 (13%) patients had survived >10 years. Of the remaining 188 patients who did not achieve CR, 13 (17%) patients who survived >5 years and only 1 (0·5%) patient survived >10 years.

CNS involvement by treatment regimen

CNS involvement was 1·6% (95% CI, 0·04–8·7) in JCOG9109, 6·3% (95% CI, 2·3–13·1) in JCOG9303, and 3·5% (95% CI, 0·4–12·1) in the VCAP-AMP-VECP arm and 8·2% (95% CI, 2·7–18·1) in the CHOP-14 arm of JCOG9801. No significant differences in the proportion of CNS involvement were observed among the regimens.

Development of the PI

In univariate analyses, three covariates showed significant associations with OS, namely PS, corrected calcium level and serum total protein (all $P < 0{\cdot}05$; Table II). Stepwise Cox regression analysis returned three unfavourable prognostic

Table I. Clinical characteristics of 15 covariates in all 276 registered patients.

		JCOG9109 (n = 62)	JCOG9303 (n = 96)	JCOG9801 (n = 118)	Total (n = 276)
Initial date of registration		November 1991	January 1994	July 1998	
Final date of registration		July 1993	December 1996	October 2003	
Number of sites		30	20	27	49
Sex	Male/female	38/24	54/42	61/57	153/123
Age, years	≥20, <30	0	1	0	1
	≥30, <40	2	7	6	15
	≥40, <50	14	29	20	63
	≥50,<60	27	24	44	95
	≥60, <70	19	35	48	102
PS	0/1	23/22	19/25	49/46	91/93
	2/3/4/NE	7/9/1/0	17/9/8/18	18/4/1/0	42/22/10/18
B symptoms	+/−/NE	22/36/4	39/57/0	45/73/0	106/166/4
Stage	I/II/III/IV	1/4/8/49	2/6/14/74	0/4/8/106	3/14/30/229
Liver invasion	+/−	10/52	20/76	25/93	55/221
LDH, iu/l	<−1 × ULN/>	9/53	10/86	20/98	39/237
BUN, mmol/l	<−1 × ULN/>/NE	47/14/1	80/15/1	107/11/0	234/40/2
Corrected Ca, mmol/l	<2·75/≥/NE	49/9/4	75/16/5	93/25/0	217/50/9
Serum protein, g/l	<60/≥/NE	18/44/0	27/69/0	30/87/1	75/200/1
Albumin g/l	<35/35–40/≥40/NE	18/26/15/3	35/39/18/4	28/64/26/0	81/129/59/1
WBC ($\times 10^9$/l)	<3/≥	48/14	77/19	104/14	229/47
Lymphocytes ($\times 10^9$/l)*	<4/4–15/≥15/NE	28/16/14/4	54/19/23/0	64/33/20/1	146/68/57/5
Neutrophils ($\times 10^9$/l)	<8/≥/NE	49/12/1	75/21/0	94/24/0	218/57/1
Platelets ($\times 10^9$/l)	<150/≥	16/46	19/77	19/99	54/222

B symptoms: fever, night sweats, and weight loss.
JCOG, Japan Clinical Oncology Group; ECOG PS, Eastern Cooperative Oncology Group performance status; Ca, calcium level; WBC, white blood cell count; ULN, upper limit of normal; NE, not evaluated.
*total (normal + abnormal) lymphocyte count.

factors associated with OS, namely a high, corrected calcium level, high PS (2–4), and the existence of B symptoms, although the third factor was not statistically significant (Table II). Table II also presents the results of the model when the two significant factors of corrected calcium and ECOG PS were included. The hazard ratios (HRs) estimated by this model were 1·574 (95% CI, 1·088–2·277; P = 0·016) for corrected calcium and 1·554 (95% CI, 1·120–2·157; P = 0·008) for ECOG PS.

The four categories consisting of the two prognostic factors (corrected calcium level and PS) were combined into a dichotomous PI, named the JCOG-PI, by considering its potential for clinical use. Similarly, we constructed a dichotomous PI including B symptoms with two prognostic factors. We excluded B symptoms from further assessment because the Akaike Information Criteria of JCOG-PI (1537·8) was smaller than that of PI (1545·6).

According to the JCOG-PI, the MST and 5-year OS were 14 months and 18% in patients with both corrected calcium <2·75 mmol/l and a PS of 0 or 1 (moderate-risk group) and were 8 months and 4% in patients with corrected calcium ≥2·75 mmol/l and/or a PS of 2–4 (high-risk group) respectively (Fig 4A). The HR and 95% CI were 1·926 and 1·423–2·606 respectively (P < 0·0001).

External validation

Nine patients in the validation set of 136 patients had missing corrected calcium or PS data, resulting in 127 evaluable patients (Fig 5). The median and longest follow-up periods were 9 months and 97 months, respectively. The HR was 2·138 (95% CI, 1·414–3·233, P = 0·0003) with an MST of 18 months and 6 months in the moderate- and high-risk groups respectively and JCOG-PI showed good reproducibility (Fig 4B).

Discussion

In this first prospective analysis of a large cohort of aggressive ATL patients from prospective clinical trials conducted after the clinical subtype classification of ATL was introduced, we constructed the JCOG-PI based on corrected calcium level and PS and validated it with external data. The ascertained discrepancy was stronger among the external validation set. In addition, OS of high-risk patients was worse in the external validation set than in the training set, probably reflecting poor organ functions and other unfavourable prognostic factors in patients not participating in clinical trials. The OS of the moderate-risk patients was better in the

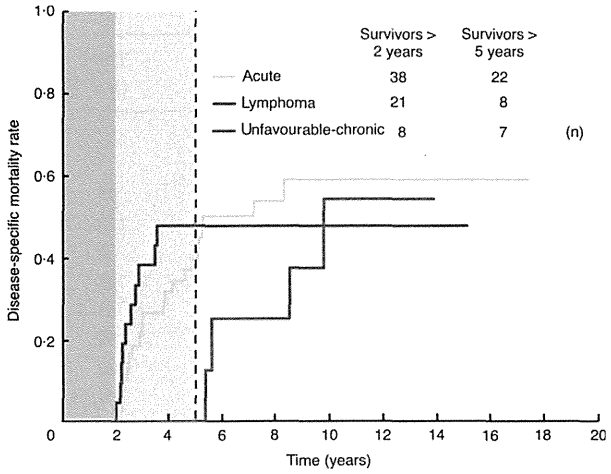

Fig 3. ATL-related deaths of patients who survived >2 years according to subtype. Among the 37 patients who survived >5 years, there were no ATL-related deaths in lymphoma type in contrast to the 10 ATL-related deaths in other types after 5 years.

external validation set than in the training set, possibly reflecting recent advances in treatment, including chemotherapy and allogeneic haematopoietic stem cell transplantation (allo-HSCT).

In our analysis of patients who survived >5 years, no ATL-related deaths occurred in those with lymphoma type, which is in contrast to the ATL-related deaths seen among patients with acute or unfavourable chronic type (Fig 3). This suggests that about 10% of patients with lymphoma type survived >5 years, most of whom might have been cured. Although abnormalities of comparative genomic hybridization might differ between acute and lymphoma types (Oshiro *et al*, 2006), the difference in clinical course between lymphoma type and acute or unfavourable chronic type remains unclear, and further analyses on the molecular and biological features of these types are needed.

Of the 276 patients studied, 20 received an allo-HSCT. The 5-year OS rate of these patients was 40%, compared with 12% in patients who did not undergo transplantation

Table II. Results of univariate and multivariate analyses in the training set (n = 193).

Factor		Univariate analysis HR (95%CI)	*P* value	Pre-planned multivariate analysis (AIC = 1545·6) HR (95%CI)	*P* value	Model used for constructing JCOG-PI (AIC = 1537·8) HR (95%CI)	*P* value
Ca, mmol/l	<2·75	Ref		Ref		Ref	
	≥2·75	1·742 (1·214–2·498)	0·002	1·688 (1·156–2·466)	0·007	1·574 (1·088–2·277)	0·016
ECOG PS	0–1	Ref		Ref		Ref	
	2–4	1·680 (1·219–2·314)	0·001	1·493 (1·073–2·078)	0·018	1·554 (1·120–2·157)	0·008
B symptoms	–	Ref		Ref			
	+	1·249 (0·926–1·685)	0·145	1·288 (0·945–1·755)	0·109		
Sex	Male	Ref					
	Female	0·999 (0·743–1·342)	0·994				
Age, years	<60	Ref					
	≥60	1·108 (0·818–1·502)	0·504				
Stage	I–II	Ref					
	III–IV	1·293 (0·682–2·451)	0·429				
Liver invasion	–	Ref					
	+	1·238 (0·867–1·768)	0·241				
LDH, iu/l	≤ULN	Ref					
	>1 × ULN	1·325 (0·840–2·091)	0·226				
BUN, mmol/l	≤ULN	Ref					
	>1 × ULN	1·332 (0·871–2·036)	0·184				
Serum protein, g/l	<60	Ref					
	≥60	0·642 (0·457–0·901)	0·010				
Lymphocytes, $\times 10^9$/l	<4	Ref					
	4–14·9 (vs. <4)	1·110 (0·785–1·570)	0·553				
	≥15 (vs. <4)	1·102 (0·747–1·626)	0·626				
Neutrophils, $\times 10^9$/l	<8	Ref					
	≥8	1·271 (0·888–1·817)	0·189				
Platelets, $\times 10^9$/l	<150	Ref					
	≥150	0·900 (0·626–1·294)	0·569				

AIC, Akaike's Information Criteria; JCOG, Japan Clinical Oncology Group; PI, Prognostic index; HR, hazard ratio; CI, confidence interval; Ref, reference; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; BUN, blood urea nitrogen.

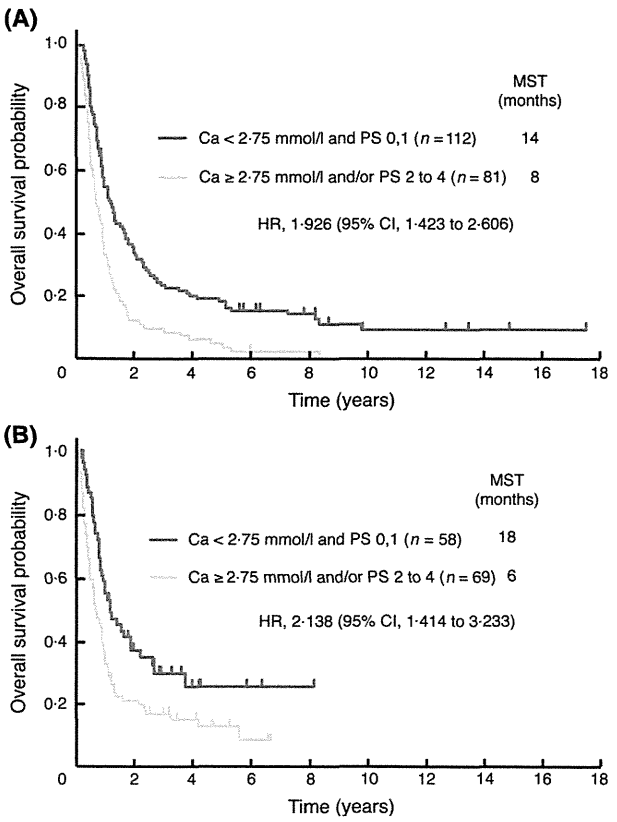

Fig 4. Overall survival of the patients in the training set and in the external validation set according to the JCOG-PI. (A) OS in the training set. The median survival time (MST) and 5-year OS were 14 months and 18% in moderate-risk group (blue line) and were 8 months and 4% in high-risk group (yellow line), respectively (B) OS in the validation set. The MST of 18 months and 6 months in the moderate- (blue line) and high-risk (yellow line) groups, respectively, and JCOG-PI showed good reproducibility.

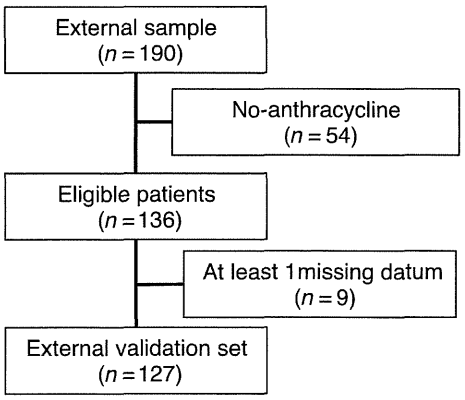

Fig 5. Patient disposition of the external validation set.

(data not shown). However, it was too difficult to evaluate the efficacy of allo-HSCT in our cohort because the disease status at transplantation and the duration from registration to transplantation were rather heterogeneous and the transition to allo-HSCT was time-dependent. To adjust this time-dependent causality, periodical data collection of, for example, indicators of treatment and time-dependent confounders, is necessary. The causal relationship between allo-HSCT and OS should be evaluated in a future prospective trial.

Several reports have revealed risk factors for ATL. In a prospective randomized trial against NHL parsimonious conducted between 1981 and 1983, Shimoyama *et al* (1988) demonstrated that poor PS and high lactate dehydrogenase levels were poor prognostic factors in patients with advanced T-cell lymphoma/leukaemia, including ATL. In a Japanese nationwide survey of 854 patients, a multivariate analysis identified major prognostic indicators of ATL as poor PS, high lactate dehydrogenase levels, age ≥40 years, >3 involved lesions and hypercalcaemia (Lymphoma Study Group, 1991). These factors were then used to construct a risk model. Additional factors reportedly associated with poor prognosis, as determined by multivariate analyses, include thrombocytopenia (Yamada *et al*, 1997), eosinophilia (Utsunomiya *et al*, 2007), bone marrow involvement (Takasaki *et al*, 2007), high interleukin (IL)5 and IL10 serum levels (Inagaki *et al*, 2006), C-C chemokine receptor 4 (CCR4) expression (Ishida *et al*, 2003), lung resistance-related protein (Ohno *et al*, 2001), *TP53* mutation (Tawara *et al*, 2006) and *CDKN2A* deletion (Yamada *et al*, 1997). Specific to chronic-type ATL, multivariate analysis has identified high lactate dehydrogenase levels, high blood urea nitrogen levels and low albumin levels as poor prognostic factors in several retrospective analyses (Shimoyama, 1994).

Recently, an ATL-PI consisting of Ann Arbour clinical stage, PS, age, serum albumin level and soluble IL2 receptor level was used to identify three risk groups for patients with acute and lymphoma types of ATL (Katsuya *et al*, 2012). However, in that study, both the ATL-PI and the risk grouping in the 1980's were constructed based on the results of questionnaires collected retrospectively; hence the treatments used were diverse and the prognostic factors might not have been evaluated homogeneously, in contrast to present study based on the three prospective trials (Lymphoma Study Group, 1991; Katsuya *et al*, 2012).

In the present study, monoclonal integration of HTLV-1 was not detected in four of 104 patients analysed. It was previously demonstrated that about 20% of patients with lymphoma-type ATL did not have monoclonal integration of HTLV-1, by Southern blot analysis, when investigating lymph node specimens (Ohshima *et al*, 1998). From this aspect, the possibility that a fraction of patients with the lymphoma type in the present study had non-ATL-peripheral T-cell lymphoma cannot be completely excluded. Further studies are required to differentiate lymphoma-type ATL from non-ATL-peripheral T-cell lymphoma by analysing monoclonal integration of the HTLV-1 provirus by Southern blot analysis or integration site-specific polymerase chain reaction.

In this study, the median age of 56 years in the training set was notably younger than that in other recent reports and that of the average population of patients with ATL. The

population investigated in the present study represents a selection of fairly young and physically fit patients with preserved organ functions. Although we expected to define a favourable prognosis group in the international PI for aggressive NHL, which consists mostly of diffuse large B-cell lymphoma, the difference in the OS between the two risk groups was small. This finding was similar to a recent retrospective nationwide survey in Japan of all patients with acute or lymphoma type at each institute (Katsuya *et al*, 2012). Therefore, the JCOG-PI could not be used to identify patients with aggressive ATL who could be treated with intensive chemotherapy alone and spared from more intensive therapy, such as allo-HSCT, as is the case with the ATL-PI (Katsuya *et al*, 2012). However, we did manage to identify patients with extremely poor prognosis despite undergoing intensive chemotherapy in clinical trials. These patients might be candidates for future trials that combine new agents or investigational strategies.

Recently, the results of several phase I and II trials using a defucosylated anti-CCR4 antibody for relapsed patients with aggressive ATL have demonstrated clinically meaningful antitumour activity and an acceptable toxicity profile (Yamamoto *et al*, 2010; Ishida *et al*, 2012a). Moreover, allo-HSCT with myeloablative and reduced intensity conditioning for patients with aggressive ATL has been reported to cure diseases associated with the graft-*versus*-ATL effect, despite the high transplant-related mortality (Hishizawa *et al*, 2010; Ishida *et al*, 2012b; Kanda *et al*, 2012). To further improve patient outcomes, two trials are ongoing in Japan: a phase II trial of VCAP-AMP-VECP followed by allo-HSCT with myeloablative conditioning for patients aged <55 years with aggressive ATL (JCOG 0907), and a randomized phase II trial of VCAP-AMP-VECP with or without anti-CCR4 antibody (Jo *et al*, 2013).

In conclusion, patients with lymphoma-type ATL who survived >5 years might have been cured, which is in contrast to long-term survivors with acute or unfavourable chronic type. The JCOG-PI, based on corrected calcium levels and PS, is a simple and valuable tool for identifying patients with aggressive ATL having extremely poor prognosis in clinical trials, and it will be useful for the design of future studies combining new drugs or investigational strategies.

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Authorship

T.F., M.S, H.F., K. T. and K.T. designed the study and wrote the paper. T.H. designed the study. S.N. and T.S. designed the study, analysed data and wrote the paper. Y.I., Y.M., T.T., K.U., Y.K., N.F., A.U., M.T., K.N., M.H., N.U., S.Y., K.T., K.I., M.K. and M.N. collected data and reviewed the paper.

Disclosure

The authors report no potential conflict of interest.

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Human T-cell Lymphotropic Virus Type I–Associated Adult T-cell Leukemia–Lymphoma: New Directions in Clinical Research

Kunihiro Tsukasaki[1] and Kensei Tobinai[2]

Abstract

Adult T-cell leukemia–lymphoma (ATL) is a distinct malignancy of regulatory T cell (Treg)/TH2 cells caused by human T-cell lymphotropic virus type I (HTLV-1), with a high frequency of expression of CD3/CD4/CD25/CCR4 and FoxP3 in about half of the cells. However, in primary ATL cells, although expression of the virus, including the Tax oncoprotein, appears just after an *in vitro* culture, integration sites of the provirus into the host genome are random, and chromosomal/genetic abnormalities are complex. ATL is thus a single disease entity that is caused by HTLV-1 and possesses diverse molecular features. The clinical features and prognosis of ATL vary, and this has led to subtypes classified into four categories: acute, lymphomatous, chronic, and smoldering types, based on lactate dehydrogenase and calcium values and organ involvement. Approximately 15 to 20 million individuals are infected with HTLV-1 worldwide, 1.1 million of whom reside in Japan, and the annual incidence of ATL has been estimated to be approximately 1,000. HTLV-1 infection early in life, mainly from breast feeding, is crucial for the development of ATL. The age-specific occurrence of ATL and complex genome abnormalities that accumulate with disease progression suggest a multistep carcinogenesis model following HTLV-1 infection. Various treatment options are available for ATL and consist of watchful waiting for indolent ATL, intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation for aggressive ATL, and a combination of IFNα and zidovudine for ATL with leukemic manifestation. Several promising new agents, including an anti-CCR4 antibody, are currently undergoing clinical trials associated with translational research.

See all articles in this *CCR Focus* section, "Paradigm Shifts in Lymphoma."

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Introduction

Adult T-cell leukemia–lymphoma (ATL) is a rare T-cell malignancy associated with human T-cell lymphotropic virus type I (HTLV-1; refs. 1–5). Several inflammatory diseases have also been associated with HTLV-1, including tropical spastic paraparesis (TSP)/HTLV-1–associated myelopathy (HAM), infective dermatitis, and HTLV-associated uveitis (6–9). Endemic areas have been identified for the virus and these diseases, including southwestern Japan, the Caribbean islands, tropical Africa, South America, the Middle East, and northern Oceania. Only a small percentage of HTLV-1 carriers infected through breast feeding develop the disease, which suggests multistep carcinogenesis (10–12). The diversity of the clinical features and prognosis of patients with this disease has led to its classification into four categories: acute, lymphomatous, chronic, and smoldering types, based on lactate dehydrogenase (LDH) and calcium values and organ involvement (13, 14). Various treatment options are available for ATL and consist of watchful waiting for indolent (smoldering and unfavorable chronic) ATL, intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) for aggressive (unfavorable chronic, lymphomatous, and acute) ATL, and a combination of IFNα and zidovudine (IFN/AZT) for ATL with leukemic manifestation. ATL is more refractory to chemotherapy than other peripheral T-cell lymphomas (PTCL), but is relatively sensitive to potential HTLV-1–targeting therapies such as allo-HSCT and IFN/AZT (12). A recent phase II trial revealed that an anti-CC chemokine receptor (CCR4) antibody was effective against relapsed ATL (15). Furthermore, other promising new agents for PTCL, including ATL, are being developed. Recent advances in clinical and translational research on this disease, including molecular, epidemiologic, biologic, and therapeutic aspects, are summarized below.

Molecular Epidemiology of ATL

The seroprevalence of HTLV-1 was examined in 1,196,321 Japanese first-time blood donors between 2006 and 2007 (16). A total of 3,787 of them were confirmed to be positive

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for the anti–HTLV-1 antibody. By applying a fitness curve to age ranges outside the blood donor age range, the present number of HTLV-1 carriers from age 0 to 99 years was estimated to be at least 1.08 million in Japan, approximately 10% lower than that reported in 1988. The adjusted overall prevalence rates of HTLV-1 were estimated to be 0.66% and 1.02% in men and women, respectively. Carrier numbers peaked among individuals in their 70s, markedly different from the previous peak observed among individuals in their 50s in the 1988 database, probably reflecting a birth cohort effect. Compared with the survey conducted in the 1980s, carriers were distributed not only in endemic regions in Japan, but throughout the country, particularly in the greater Tokyo metropolitan area (16). A high prevalence of HTLV-1 is also found in the Caribbean islands (African), tropical Africa (African), South America (Mongoloid), and northern Oceania (Melanesian; refs. 10, 11).

The three major routes of HTLV-1 transmission are mother-to-child infections (via breast milk), sexual intercourse, and blood transfusions (10, 11). The overall infection rate of HTLV-1 in children by seropositive mothers was previously estimated to be between 10% and 30% mainly through breast feeding (17). The reported risk factors for the development of ATL among HTLV-1 carriers include HTLV-1 infection early in life, an increase in age, male sex, family history of ATL, past history of infectious dermatitis, smoking, serum titers of the antibody against HTLV-1, HTLV-1 proviral load, and several HLA subtypes (11, 18). However, these were the findings of relatively small and not-comprehensive studies. A total of 1,218 asymptomatic HTLV-1 carriers (426 males and 792 females) were examined between 2002 and 2008 for a prospective cohort-study on the development of ATL in Japan (19). The proviral load at enrollment was significantly higher in males than in females [median, 2.1 vs. 1.4 copies/100 peripheral blood mononuclear cells (PBMC)], in those ages 40 or older, and in those with a family history of ATL. During the follow-up period, 14 participants developed acute ATL. Their baseline proviral loads were high (range, 4.2–28.6 copies/100 PBMC). Not only a higher proviral load, but also advanced age, family history of ATL, and the first opportunity for HTLV-1 testing during the treatment of other diseases were independent risk factors for the progression of ATL.

Although the incidence of ATL in HTLV-1–endemic areas is known to be high, population-based evidence concerning the incidence of ATL in nonendemic areas is scarce. Chihara and colleagues recently estimated the age-standardized incidence of ATL between 1993 and 2006 in Japan and between 1993 and 2008 in the United States, and assessed trends using a population-based cancer registry in Japan and Surveillance Epidemiology and End Results in the United States (20). A total of 2,055 patients in three prefectures in Kyushu and 1,380 patients in 12 prefectures in Honshu were diagnosed with ATL during the study period. In the United States, a total of 140 patients were diagnosed with ATL. This study showed that the age-standardized incidence in nonendemic areas in Japan and the United States significantly increased during this period [annual percentage change (95% confidence interval; CI); Japan-Honshu: +4.6% (1.1–8.2); U.S.: +6.2% (1.5–11.1)], whereas no change was observed in endemic areas in Japan (Japan-Kyushu: 0.0%; 1.6–1.7).

Biology of HTLV-1–Associated ATL

The HTLV-I gene encodes three structural proteins: Gag, Pol, and Env, and complex regulatory proteins such as Tax, which not only activate viral replication, but also induce the expression of several cellular genes important in the proliferation and antiapoptosis of ATL cells, including NF-κB (Fig. 1; refs. 5, 21, 22). The expression of these cellular proteins may enhance the multistep carcinogenesis of ATL, whereas expression of the viral proteins *in vivo* is suppressed by cytotoxic T cells. A new viral factor, HTLV-1 basic Zip factor (HBZ), which was encoded from the minus strand of mRNA, was recently discovered and may play a role in viral replication and T-cell proliferation because it is steadily expressed in most HTLV-1–infected cells and primary ATL cells whereas Tax is not (23). The polycomb-mediated epigenetic silencing of miR31 was more recently reported to be implicated in the aberrant and constitutive activation of NF-κB signaling in ATL cells (24). HBZ and miR31 may be good targets for the prevention as well as treatment of ATL.

ATL is a distinct malignancy of regulatory T cell (Treg)/TH2 cells caused by HTLV-1 with high frequency of expression of CD3/CD4/CD25/CCR4 and FoxP3 in about half of the cells (25, 26).

Figure 2 summarizes the multistep leukemogenesis of ATL, which consists of viral, epigenetic, and genetic factors. Regarding the viral factors, Tax, which is a strong transactivating factor of host genes and important in cell transformation, is considered to be crucial for the oligoclonal maintenance and expansion of HTLV-1–infected cells in the early phase of HTLV-1–infected individuals, the so-called healthy HTLV-1 carriers (10, 11, 22). However, the expression of Tax, which is very immunogenic, should be transient on each HTLV-1–infected cell escaping the immune surveillance of the host. Thereafter HTLV-1–infected cells can transform with a combination of the continued expression of HBZ, acquired epigenetic regulation of cell-transforming factors, full-blown development of ATL with the genetic/epigenetic loss of function of tumor suppressor genes and microRNAs (miRNA), and activation of oncogenes (12, 23, 24, 27–34). These abnormalities are acquired during the progression of ATL from the indolent to the aggressive subtypes. These abnormalities, excluding Tax, HBZ, and miR31, are very diverse, as revealed by the aneuploidy profile obtained using comparative genomic hybridization and microarray expression profile (35, 36). These findings indicated that ATL is a single disease entity associated with HTLV-1 that acquires diverse molecular abnormalities resembling the acute-crisis phase of chronic myeloid leukemia with similar diverse abnormalities caused by bcr/abl. Clonal selection during the progression of ATL is typically the consequence of clonal evolution.

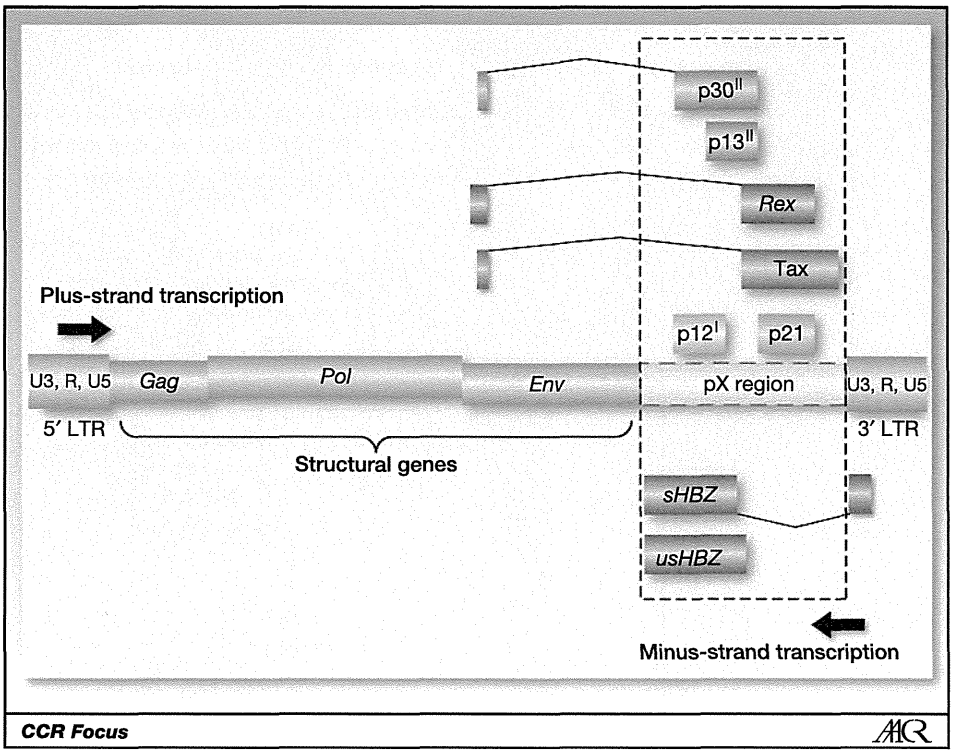

Figure 1. The structure of HTLV-1. The HTLV-I gene encodes three structural proteins, Gag, Pol, and Env, and complex regulatory proteins such as Tax, which not only activate viral replication, but also induce the expression of several cellular genes (5, 21). The expression of these viral proteins *in vivo* is suppressed by CTLs. HTLV-1 basic Zip factor (HBZ), encoded from the minus-strand mRNA, may play a role in viral replication and T-cell proliferation because it is steadily expressed in most HTLV-1–infected cells and primary ATL cells, whereas Tax is not. Reprinted with permission from Satou and Matsuoka (21).

Multiple subclones in lymph nodes originate from a common clone in many ATL cases, and a selected subclone among the lymph node subclones appears in the peripheral blood (37). Clonal changes, but not clonal evolution, have been reported in approximately 10% of cases progressing from indolent to acute ATL, and may reflect the emergence of multiple premalignant oligoclones in viral leukemogenesis, as suggested in Epstein–Barr virus-associated lymphomagenesis in immunocompromised hosts (38, 39). The genomic characteristics of proviral integration sites in malignant and nonmalignant clones, as well as the proviral features (genomic structure and 5′LTR methylation) that determine its capacity to express Tax, were recently identified using a sensitive high-throughput method for primary ATL cells (40).

ATL lesions in the peripheral blood are morphologically diagnosed in the same manner as other lesions involving the lymph nodes (13, 14). However, ATL cell atypia vary from the so-called flower cells with multilobulated nuclei to chronic lymphocytic leukemia (CLL)–like cells resembling normal lymphocytes (41). The monoclonal integration of HTLV-1 detected by Southern blotting hybridization (SBH) is used as a supportive method for the diagnosis of ATL with a threshold sensitivity of approximately 5%. However, SBH can also detect monoclonal integration in a small percentage of HTLV-1 carriers and approximately 10% of HAM/TSP patients (42, 43). Flow-cytometric analysis of T cells recently revealed that the expression of CADM1 and stepwise downregulation of CD7 were closely associated with the clonal expansion of HTLV-1–infected cells in ATL, and $CADM1^+$ cells with the downregulated expression of CD7 in asymptomatic HTLV-1 carriers exhibited common properties to those in indolent ATL carriers (44).

Treatment and Prognosis of ATL

The prognosis of ATL is worse than that of other PTCLs (45). The clinical subtype classification of ATL is very useful for decision making about the treatment of each patient (13). However, there is no plateau—rather an initial steep slope and subsequent gentle slope in the survival curves of aggressive and indolent ATL treated with chemotherapy and watchful waiting, respectively, although the prognosis of the latter is markedly better [median survival time (MST), 1 year vs. 5 years; refs. 13, 46]. Improved prognostic systems have been sought. From North America, a new prognostic score for ATL was reported, based on performance status (PS), stage, age, and calcium level at diagnosis (47). A recent retrospective survey in Japan on 807 patients with acute or lymphomatous ATL treated with chemotherapy, but not with allo-HSCT, developed a prognostic index based on five prognostic factors: stage, PS, age, serum albumin, and soluble IL2 receptor (48). In the validation sample, the index was reproducible with MSTs of 3.6, 7.3, and 16.2 months for patients at high, intermediate, and low risk, respectively. The Japan Clinical Oncology Group (JCOG)-Lymphoma Study Group (LSG) conducted a meta-analysis of three consecutive trials exclusively for aggressive ATL (see below; ref. 49). An overall survival (OS) analysis of 276 patients with aggressive ATL identified two significant prognostic factors, PS and hypercalcemia. In the validation sample, a proposed prognostic index using these two factors

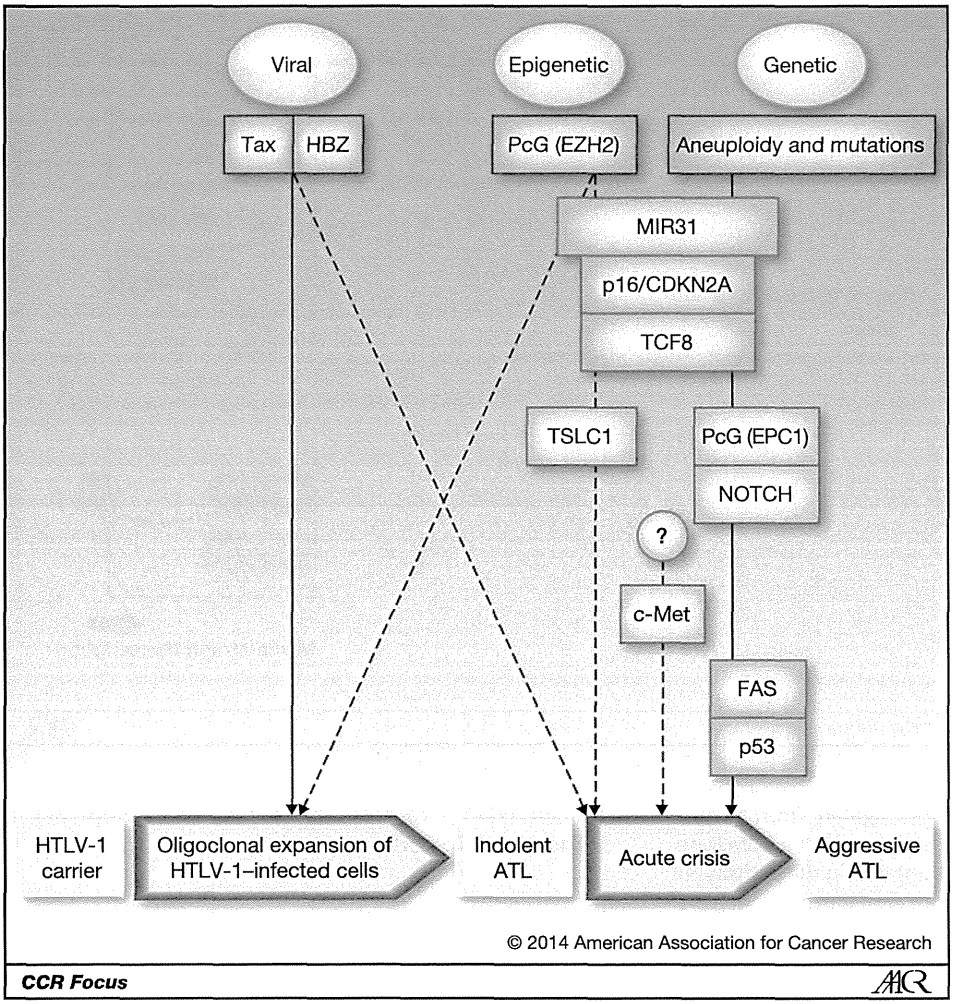

Figure 2. The role of viral, epigenetic, and genetic factors in the multistep leukemogenesis of ATL. Tax is considered crucial for the oligoclonal maintenance and expansion of HTLV-1–infected cells in early phase with the expression transient on each HTLV-1–infected cells escaping from the immune surveillance of hosts. Thereafter, continuing expression of HBZ, acquired epigenetic regulation of cell-transforming factors is followed by genetic/epigenetic loss of function of tumor suppressor genes and miRNAs, and activation of oncogenes (12, 23, 24, 27–34). Diverse abnormalities are acquired during the progression of ATL from indolent to aggressive disease.

in two strata revealed MSTs of 6.3 and 17.8 months for patients at high and low risk, respectively. However, the 5-year OS rates in both studies were less than 15%, even in the low-risk group; therefore, the subgroup with relatively favorable prognoses could not be identified. However, approximately 10% of patients with lymphoma-type ATL survived more than 10 years without allo-HSCT, which suggests that they may have been cured (49).

JCOG-LSG has consecutively conducted clinical trials on aggressive non-Hodgkin lymphoma (NHL), including ATL (50). Aggressive ATL has been exclusively studied from other NHLs after far worse response and survival rates were reported in earlier studies. A phase II trial (JCOG9303) for aggressive ATL using the LSG15 regimen, which consisted of six cycles of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) with the prophylactic use of G-CSF and intrathecal prophylaxis, revealed a promising response rate and MST. After JCOG9303, we conducted a phase III trial to compare modified (m)-LSG15 (VCAP-AMP-VECP) with CHOP-14, both supported by G-CSF and intrathecal prophylaxis. A higher 3-year survival rate (24% vs. 13%) and complete response rate (40% vs. 25%) with mLSG15 than with CHOP-14 suggested that the former was a more effective regimen at the expense of greater toxicities, which provided the basis for future investigations on the treatment of aggressive ATL (51). However, the MST of 13 months is still unsatisfactory.

A treatment strategy for ATL based on clinical subtypes, prognostic factors, and response to the initial therapy was suggested in an international consensus report (52). Patients with aggressive ATL generally have a very poor prognosis due to the multidrug resistance of ATL cells, large tumor burden with multiorgan failure, hypercalcemia, and/or opportunistic infections (10–13). Intensive chemotherapy such as mLSG15 is recommended for aggressive ATL (51, 52). Watchful waiting until disease progression has been recommended for indolent ATL, although the long-term prognosis of this disease was inferior to that of, for example, CLL (46, 52). Treatment decisions should be based on the ATL subclassification and the prognostic factors at onset and response to initial therapy (Table 1). The prognostic factors include clinical factors, such as PS, LDH, age, stage, number of involved lesions, and hypercalcemia, and molecular factors, such as Ki-67 expression, solubile IL2 receptor,

Table 1. Strategy for the treatment of adult T-cell leukemia–lymphoma proposed from an international consensus meeting

Smoldering- or favorable chronic-type ATL.
- Consider inclusion in prospective clinical trials.
- Symptomatic patients (skin lesions, opportunistic infections, and so on): consider AZT/IFNα or watch and wait.
- Asymptomatic patients: consider watch and wait.

Unfavorable chronic- or acute-type ATL.
- Recommend: inclusion in prospective clinical trials.
- If outside clinical trials, check prognostic factors (including clinical and molecular factors if possible):
  - Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a randomized phase III trial against biweekly CHOP) or AZT/IFNα (evaluated by a retrospective worldwide meta-analysis).
  - Poor prognostic factors: consider chemotherapy followed by conventional or reduced-intensity allogeneic HSCT (evaluated by retrospective or prospective Japanese analyses, respectively).
  - Poor response to initial therapy with chemotherapy or AZT/IFNα: consider conventional or reduced-intensity allogeneic HSCT.

Lymphoma-type ATL.
- Recommend: inclusion in prospective clinical trials.
- If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP).
- Check prognostic factors and response to chemotherapy (including clinical and molecular factors if possible):
  - Favorable prognostic profiles and good response to initial therapy: consider chemotherapy.
  - Unfavorable prognostic profiles or poor response to initial therapy with chemotherapy: consider conventional or reduced-intensity allogeneic HSCT.

Options for clinical trials (first line).
- Test the effect of up-front allogeneic HSCT.
- Test promising targeted therapies such as arsenic trioxide + IFNα, bortezomib + chemotherapy, or antiangiogenic therapy.
- Consider a phase II global study testing pegylated IFN and AZT.

Options for clinical trials (relapse or progressive disease).
- Test the effect of promising targeted therapies such as arsenic trioxide and IFNα, bortezomib, a purine nucleotide phosphorylase inhibitor, histone deacetylase inhibitors, monoclonal antibodies, antiangiogenic therapy, and survivin, β-catenin, syk, and lyn inhibitors, etc.
- Consider conventional or reduced-intensity allogeneic HSCT when possible.

Abbreviation: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

alteration of p53 or p15INK4B/p16INK4A, and overexpression of IRF-4 (47–49, 52). Initial relatively small phase II studies and recent retrospective meta-analyses suggested that IFN/AZT therapy may be promising, especially for types with leukemic manifestation (53–55). The therapeutic effects of IFN/AZT are not considered to be attributable to direct cytotoxic effects on leukemic cells (56). A possible mechanism of the combination for ATL includes AZT treatment of ATL cell lines resulting in telomere attrition, which reprograms cells to undergo p53-dependent senescence, and IFN alone suppressing the expression of HTLV-1 and cell cycling, whereas IFN/AZT induces p53 signaling and apoptosis in HTLV-1–infected cells (57, 58).

Allo-HSCT is promising for the treatment of aggressive ATL, possibly reflecting graft-versus-ATL effect, including the nonmyeloablative conditioning regimen (59–61). Minimal residual disease following allo-HSCT, which is detected as the HTLV-1 proviral load, was markedly less than that after chemotherapy or AZT/IFN therapy, which suggested the presence of a graft-versus-ATL effect as well as graft-versus-HTLV-1 activity (62). ATL with abnormalities in tumor suppressor genes such as p53 was reportedly resistant to IFN/AZT therapy as well as chemotherapy. Allo-HSCT may overcome this resistance (52). It remains unclear which type of allo-HSCT (myeloablative or reduced intensity conditioning) is more suitable for the treatment of ATL. Furthermore, selection criteria with respect to responses to previous treatments, the sources of stem cells, and the HTLV-1 viral status of the donor have yet to be determined.

Translational Research and Clinical Trials of New Agents for ATL

Translational research is mandatory for the development of new agents against specific disease subtypes such as PTCLs, including ATL. Research on the biology of HTLV-1–infected cells and ATL cells revealed that the IL2, IL9, IL15

pathways in conjunction with the JAK–STAT or Wnt pathways are crucial in this disease (63). Several mouse models of ATL development exist, including NOG mice in which the growth and proliferation of the primary cells of aggressive and indolent ATL are marked and resemble the site of organ involvement and hypercalcemia, thymus-derived leukemia–lymphoma in mice transgenic for the Tax gene, and an HTLV-1–infected intra-bone marrow injection of human $CD133^+$ stem cells into a NOG mouse model to recapitulate distinct ATL-like symptoms as well as HTLV-1–specific immune responses (64–66). These mouse models are useful for translational research on ATL; for example, the synergistic effects of the combination of IFN/AZT with As(2)O(3) were reported in a Tax transgenic mouse model (67).

Several promising new agents for ATL are currently undergoing translational research and some are now in clinical trials. Among them are an anti-CCR4 antibody, mogamulzumab, which has been approved for relapsed/refractory ATL in Japan; a CD30-directed antibody–drug conjugate, brentuximab vedotin, which is being assessed in a global phase III trial with chemotherapy for untreated PTCLs, including ATL; and an immunomodulatory agent, lenalidomide, which is in phase II testing for relapsed aggressive ATL.

Histone deacetylase inhibitors

Gene expression governed by epigenetic changes is crucial to the pathogenesis of cancer. Histone deacetylases are enzymes that are involved in the remodeling of chromatin, and play a key role in the epigenetic regulation of gene expression. The histone deacetylase inhibitor (HDACi) LBH589 exhibits significant anti-ATL effects by activating a novel RAIDD–caspase-2 pathway *in vitro* and in mice with the expression modulation of ATL-related proteins, including Tax and CCR4 (68). However, a phase II study of LBH589 for CTCL and indolent ATL was terminated because of severe infections associated with the shrinkage of skin tumors and formation of ulcers in patients with ATL. Romidepsin, another HDACi, was recently approved for the treatment of relapsed/refractory PTCL by the FDA. Further studies are needed to evaluate the efficacy of HDACis for PTCL/cutaneous T-cell lymphoma (CTCL), including ATL.

Proteasome inhibitors

The proteasome inhibitor bortezomib suppresses the activation of NF-κB, which is constitutively expressed in all subtypes of ATL cells and HTLV-1–infected cells, and has been implicated in oncogenesis as well as resistance to anticancer agents and apoptosis. This agent effectively inhibits the growth of ATL cells both *in vivo* and *in vitro* (69). A phase II study of bortezomib is now ongoing for ATL in Japan.

CD30-directed antibody–drug conjugates

The TNF receptor family member CD30 is an activation marker of lymphocytes, and signaling through CD30 is associated with cell proliferation. Some PTCLs, including ATL, as well as Hodgkin lymphoma and anaplastic large-cell lymphoma (ALCL), express CD30. Most ATL cells in less than 10% of ATL cases express CD30, similar to ALCL, whereas several to 10% of ATL cells express CD30 in the remaining ATL cases (14). To enhance the antitumor activity of CD30-directed therapy, the antitubulin agent monomethyl auristatin E was attached to a CD30-specific mAb by an enzyme-cleavable linker to produce the antibody–drug conjugate brentuximab vedotin (SGN-35). Brentuximab vedotin induced durable objective responses with acceptable toxicities in most patients with relapsed or refractory CD30-positive Hodgkin lymphoma/ALCL in several phase I and II studies (70). Regarding newly diagnosed CD30-positive PTCLs, including ATL, a phase I study of brentuximab vedotin + CHP, in which VCR was omitted to avoid its additive neurotoxicity, revealed promising results (71).

Anti-CCR4 antibody

CCR4 is expressed on the neoplastic cells of most patients with ATL, and this expression has been associated with the cutaneous manifestation and poor prognosis. The aberrant expression of Fra-2 promotes that of CCR4 and cell proliferation in ATL cells (72). The defucosylated humanized anti-CCR4 mAb (mogamulizumab), the ADCC activity of which was stronger than that of the usual antibody in preclinical analysis using primary ATL and effector cells, was approved for the treatment of relapsed/refractory ATL in Japan based on the results of phase I and II studies, with a response rate of approximately 50% and manageable toxicities, including moderate to severe skin reactions (15, 73, 74). The findings of a subsequent randomized phase II study on intensive chemotherapy (mLSG15) ± mogamulizumab for untreated aggressive ATL have recently been reported (75). This combination was anticipated because the former was more effective for ATL cells in lymph nodes than those in the peripheral blood, whereas the opposite was true for the latter (15, 51). The combination was well tolerated and produced a higher complete response rate [52% (95% CI, 33–71) vs. 33% (CI, 16–55)], respectively. Clinical trials of mAbs for ATL and other PTCLs include a humanized anti-CD52 mAb (alemtuzumab) and a humanized anti-CD2 mAb (siplizumab).

Other new agents

Other new agent trials for ATL and/or PTCL that are ongoing or in preparation in Japan include studies of IL2 fused with the diphtheria toxin targeting CD25; a novel purine nucleoside phosphorylase inhibitor, forodesine; an anti-folate, pralatrexate, an FDA-approved agent with clinical activity in T-cell malignancies, including ATL; an organic arsenic; and the immunomodulatory agent lenalidomide (76).

Conclusions

ATL cases are separately treated on the basis of the aggressive-versus-indolent subtypes, with prompt treatment using combination chemotherapy, followed by

allo-HSCT versus watchful waiting until disease progression, respectively. Therefore, future issues to be resolved in the treatment of this intractable disease with diverse clinical features include new standard treatments between watchful waiting and intensive chemotherapy ± allo-HSCT. IFN/AZT and mogamulizumab are promising treatment options, especially for aged patients. Another aspect is multimodality treatments for ATL with an extremely poor prognosis.

Two prospective studies are ongoing for ATL by JCOG-LSG. One is a phase II study of mLSG15 and mogamulizumab followed by allo-HSCT with myeloablative or non-myeloablative conditioning for aggressive ATL (JCOG0907). The other is a phase III trial for indolent ATL to compare IFN/AZT with watchful waiting (JCOG1111).

Furthermore, as described in more detail in the *CCR Focus* article by O'Connor and colleagues (77), more than 10 promising new agents for PTCL/CTCL, including ATL, are undergoing clinical trials or are in preparation with translational research. Future clinical trials on ATL should be carefully and appropriately conducted to ensure that the international consensus on ATL management is continually updated to establish evidence-based practical guidelines.

Disclosure of Potential Conflicts of Interest

K. Tsukasaki reports receiving commercial research grants from Celgene, Kyowa-Kirin, and Takeda. K. Tobinai reports receiving commercial research grants from Celgene, Kyowa-Kirin, Mundipharma, and Takeda. No other potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: K. Tsukasaki, K. Tobinai
Development of methodology: K. Tobinai
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Tsukasaki, K. Tobinai
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K. Tsukasaki, K. Tobinai
Writing, review, and/or revision of the manuscript: K. Tsukasaki, K. Tobinai
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Tsukasaki, K. Tobinai
Study supervision: K. Tobinai

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