表2 JCOG版ATLに対する治療効果判定規準[22]

【ベースラインで標的病変が存在する場合】

総合効果	評価項目							
	標的病変		非標的病変		骨髄浸潤	末梢血病変（異常リンパ球）	皮膚病変	新病変
	節性	節外性	節性	節外性				
CR	正常	消失	正常	消失	陰性	正常	正常	なし
PR	SPDの50%以上の縮小		正常 or 非増大	消失 or 非増大	問わない（未検可）	正常 or 減少	正常 or 縮小	なし
SD	CR，PR，PDのいずれにも判定されない							
PD	以下のいずれか1項目でも満たした場合にPDと判定する							
	SPDの50%以上の増大 or 節性標的病変の再腫大 or 節外性標的病変の再出現		増大 or 再腫大	増大 or 再出現	陽性化	増加	増大 or 再出現	あり

上記の項目のいずれかでも評価不能であれば総合評価は「評価不能 not evaluable（NE）」とする。

【ベースラインで標的病変が存在しない場合】

総合効果	評価項目					
	非標的病変		骨髄浸潤	末梢血病変（異常リンパ球）	皮膚病変	新病変
	節性	節外性				
CR	正常	消失	陰性	正常	正常	なし
PR*	正常 or 非増大	消失 or 非増大	問わない（未検可）	正常 or 減少	正常 or 縮小	なし
SD	CR，PR，PDのいずれにも判定されない					
PD	以下のいずれか1項目でも満たした場合にPDと判定する					
	増大 or 再腫大	増大 or 再出現	陽性化	増加	増大 or 再出現	あり

上記の項目のいずれかでも評価不能であれば総合評価は「評価不能 not evaluable（NE）」とする。
*CRの規準を満たす場合，総合効果はCRとする。

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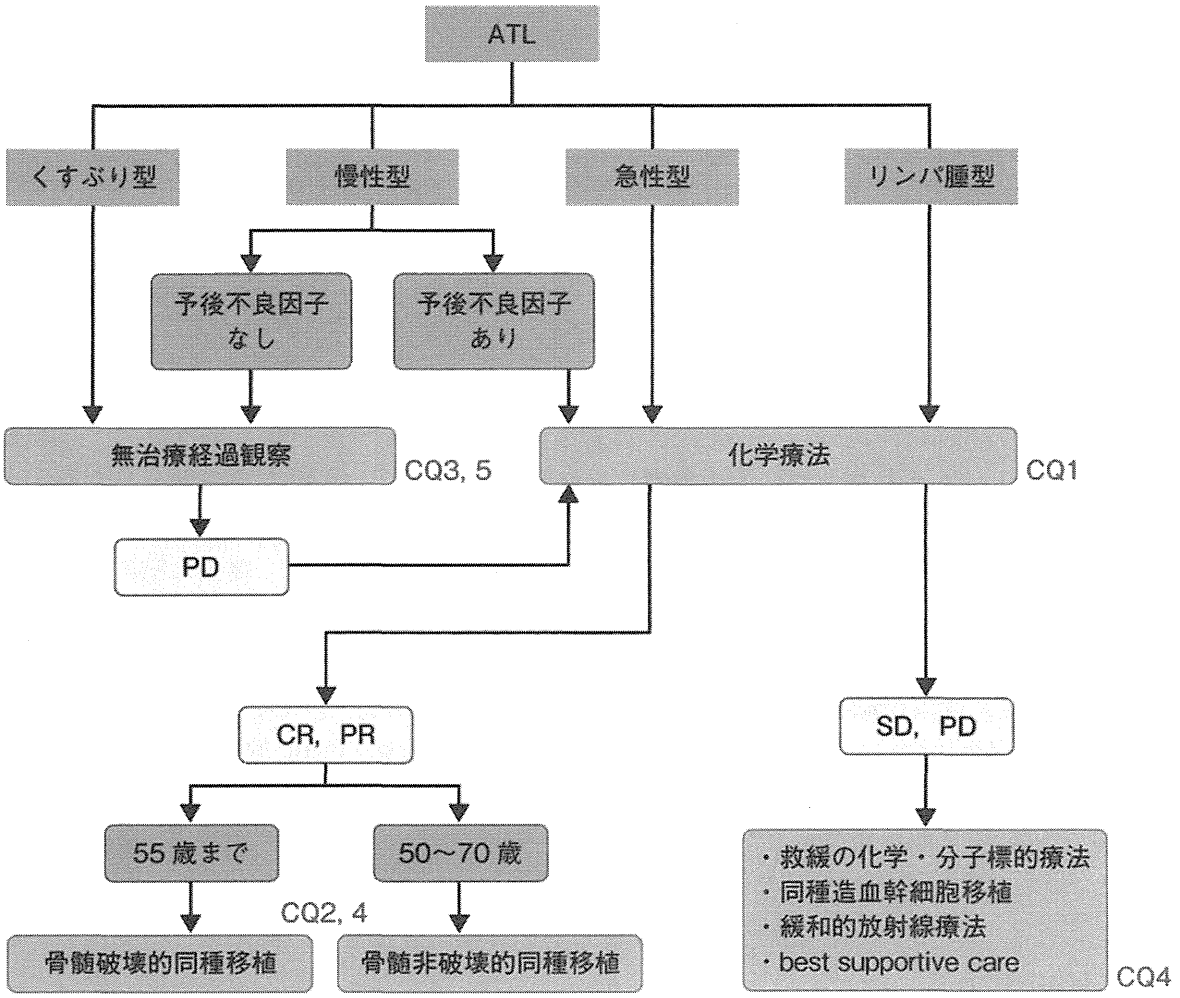
◆ アルゴリズム



急性型，リンパ腫型，予後不良因子（LDH，アルブミン，BUN いずれか一つ以上が異常値）をもつ慢性型，すなわちアグレッシブ ATL に対しては多剤併用化学療法を施行する（CQ1）。そして治療反応性が得られ，年齢・全身状態・主要臓器機能に問題がなく，適切なドナーが見つかった場合は同種造血幹細胞移植（allogeneic hematopoietic stem cell transplantation : allo-HSCT，同種移植）を検討する（CQ2, CQ4）。

くすぶり型，予後不良因子を有していない慢性型，すなわちインドレント ATL に対してはアグレッシブ ATL へ進展するまで無治療経過観察する（CQ3, CQ5）。増悪した後は初発のアグレッシブ ATL と同様に治療する。

CQ 1 初発アグレッシブ ATL に対して最も推奨される治療法は何か

推奨グレード
カテゴリー 1

VCAP-AMP-VECP 療法が最も推奨される。

解 説

1970 年代から 1980 年代にかけて，JCOG-LSG による臨床試験では ATL に対し非ホジキンリンパ腫と同様の化学療法が行われ，その MST は約 8 ヵ月と極めて予後不良であった[1)~3)]。1991 年 JCOG-LSG より ATL の臨床病型分類が提唱された後，アグレッシブ ATL を対象とした臨床試験が継続的に行われてきた。まず 1991 年から，単剤で再発・再燃 ATL に対して治療反応性がみられた[4)] ペントスタチンを組み入れた化学療法の第Ⅱ相試験が行われたが，従来の治療成績を上回らなかった[5)]。1994 年から行われた 8 つの抗がん剤を用い，G-CSF を用いて治療強度を高め，メトトレキサート（MTX）とプレドニゾロン（PSL）の髄注を併用した LSG15 療法の第Ⅱ相試験では，それまでの ATL の治療成績と比較して良好な成績が得られた[6)]。そして 1998 年から VCAP（VCR, CPA, DXR, PSL）-AMP（DXR, MCNU, PSL）-VECP（VDS, ETP, CBDCA, PSL）（modified LSG15）療法と，非ホジキンリンパ腫の標準治療の一つと当時みなされていた CHOP-14 療法とを比較する第Ⅲ相試験（JCOG9801）が行われ，VCAP-AMP-VECP 療法は血液毒性は高いものの CHOP-14 療法よりも完全奏効割合と全生存割合に優れており，ATL に対する標準治療と考えられる[7)]。ただ，この臨床試験は 70 歳未満を対象としたため，高齢者への適用の可能性に関しては不明である。

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CQ 2 アグレッシブATLに対する同種造血幹細胞移植は有用か

推奨グレード
カテゴリー2A

ATLに対する初回治療に反応性がみられた症例に対しては，HLA一致血縁，非血縁ドナーが得られた場合，同種造血幹細胞移植は長期生存が期待できる治療法として推奨される。

解　説

ATLに対する同種造血幹細胞移植（allogeneic hematopoietic stem cell transplantation：allo-HSCT）は，自家造血幹細胞移植併用大量化学療法では再発が極めて高率であるのに対し，当初単施設からの少数例の報告で化学療法では得難い長期生存例が確認された。その後に多施設後方視的解析の結果から，1年全生存割合（OS）50～52%，3年OSが45%と有望な成績が報告された[1)~4)]。そして大規模な後方視的調査として日本のデータベースを基に，allo-HSCTが施行されたATL 386例の3年OSが33%と報告された[5)]。

これらはallo-HSCTを施行し得たという選択された一群に対してではあるが，化学療法単独と比較して有望な治療成績である。移植片対宿主病（graft-versus-host disease：GVHD）合併症例において再発率が低いこと，移植後再発例において免疫抑制剤の減量・中止により再寛解に到達した症例があることなどから，移植片対ATL（graft-versus-ATL：GvATL）効果が有望な治療成績の要因の一つと考えられる。ATLに対する初回治療後に治療反応性がみられた症例には，HLA一致血縁ドナー，非血縁ドナーが得られた場合，allo-HSCTは長期生存，さらには治癒が期待できる治療法として推奨される。ただしいずれの報告でもGVHD，感染症などによる高い治療関連死亡（TRM）が示されており，化学療法後に長期奏効が得られる場合も稀にはあるため，患者へは十分な情報の提供が必要である。

allo-HSCTで骨髄破壊的前処置もしくは骨髄非破壊的前処置のいずれを選択するかについて明確なデータはないが，年齢で分けることが一般的である。骨髄破壊的前処置の対象年齢の上限は55歳，そして骨髄非破壊的前処置は50～70歳（非血縁の場合は65歳まで）を対象とすることが実臨床と臨床試験では行われている[6)~8)]。近年，血縁HTLV-1キャリアドナーからのallo-HSCT施行後に，ドナーHTLV-1感染細胞由来の再発例が報告された[9)]。その後，日本造血細胞移植学会から，血縁キャリアをドナーとする場合には末梢血を用いたHTLV-1のサザンブロット解析でモノクローナル/オリゴクローナルでないこと，臨床的にATLくすぶり型でなくHTLV-1キャリアに留まることを確認することが推奨されている[10)]。

ATLに対するallo-HSCTは，化学療法では得難い長期生存例が観察されており有効な治療法と言える。しかし，ドナーの選択，前処置法，高い移植関連死亡を減少させる感染症予防の方法などコンセンサスが得られていない課題も多い。現在日本で，アグレッシブATLに対するallo-HSCTの臨床試験が進行中である。

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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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CONFLICT OF INTEREST: None.

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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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Biology and treatment of HTLV-1 associated T-cell lymphomas

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Adult T-cell leukemia-lymphoma (ATL) is a distinct peripheral T-lymphocytic malignancy associated with human T-cell lymphotropic virus type I (HTLV-1) endemics in several regions of the world including the south-west Japan. The three major routes of HTLV-1 transmission are mother-to-child infections via breast milk, sexual intercourse, and blood transfusions. A HTLV-1 infection early in life, presumably from breast feeding, is crucial to the development of ATL. The estimated cumulative risk of developing ATL among HTLV-1-positive individuals is about 3% after transmission from the mother. The diversity in clinical features and prognosis of patients with this disease has led to its subtype-classification into acute, lymphoma, chronic, and smoldering types defined by organ involvement, lactate dehydrogenase (LDH) and calcium values. For the acute, lymphoma and unfavorable chronic subtypes (aggressive ATL), and the favorable chronic and smoldering subtypes (indolent ATL), intensive chemotherapy followed by allogeneic stem cell transplantation and watchful waiting until disease progression has been recommended, respectively, in Japan. A retrospective analysis suggested that the combination of interferon alpha and zidovudine was promising for the treatment of ATL, especially for leukemic subtypes. There are several new trials for ATL, including a defucosylated humanized anti-CC chemokine receptor 4 monoclonal antibody, histone deacetylase inhibitors, a purine nucleoside phosphorylase inhibitor, a proteasome inhibitor and lenalidomide.

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Introduction

Adult T-cell leukemia (ATL) was first described in 1977 by Uchiyama and Takatsuki as a distinct progressive T-cell leukemia of peculiar morphology, so called "flower cells" with a suspected viral etiology because of the clustering of the disease in the southwestern region of Japan [1]. Subsequently, a novel RNA retrovirus, human T-cell leukemia/lymphotropic virus type I (HTLV-1), was isolated from a cell line established from leukemic cells of an ATL patient, and the finding of a clear association with ATL led to its inclusion among human carcinogenic pathogens [2–5]. In the mid-1980s and 1990s, several inflammatory diseases were reported to be associated with HTLV-1 including tropical spastic paraparesis (TSP)/HTLV-1-associated myelopathy (HAM), HTLV-1 uveitis and infective dermatitis [6–9]. At the same time, endemic areas for the virus and diseases have been found such as the Caribbean islands, tropical Africa, South America, Mid East and northern Oceania [10]. Subsequently, diversity in the clinical features of ATL has been recognized including ATL without leukemic manifestation and nomenclature of adult T-cell leukemia/lymphoma (ATLL) and/or adult T cell leukemia-lymphoma (ATL), and a classification of clinical subtypes of the disease was proposed [11]. This chapter will review the current recognition of ATL focusing on the biology and treatment of the disease.

Recent epidemiological findings of HTLV-1 and ATL in Japan

It has been estimated that there are several tens of million HTLV-1-infected individuals reside in the world, with 1.1 million in Japan, and the annual incidence of ATL is approximately 1,000 in Japan. The annual rate of ATL development among HTLV-1 carriers older than 40 years is estimated at 1.5 per 1000 in males and 0.5 per 1000 in females, and the cumulative risk of ATL development among HTLV-1 carriers is estimated to be 2.5%–5% over the course of a 70-year life span [12].

Recently, the prevalence of HTLV-1 in Japan as determined by screening of blood donors was surveyed [13]. The seroprevalence of HTLV-1 among 1,196,321 Japanese first-time blood donors from 2006 to 2007 was investigated. A total of 3787 such donors were confirmed to be positive for the anti-HTLV-1 antibody. This resulted in an estimation of at least 1.08 million current HTLV-1 carriers in Japan, which is 10% lower than that reported in 1988. The adjusted overall prevalence rates were estimated to be 0.66% and 1.02% in men and women, respectively. The peak in carrier numbers was found among individuals in their 70s, which is a shift from the previous peak observed in the 1988 database among individuals in their 50s. As compared to the survey in the 1980s, carriers were distributed throughout the country, particularly in the greater Tokyo metropolitan area.

Factors reportedly associated with the onset of ATL include the following: HTLV-1 infection early in life, increase in age, male sex, family history of ATL, past history of infective dermatitis, smoking of tobacco, serum titers of antibody against HTLV-1, HTLV-1 proviral load and several HLA subtypes [10,14]. However, definitive risk factors for the development of ATL among asymptomatic HTLV-1 carriers have not been elucidated. Recently, Iwanaga and colleagues evaluated 1218 asymptomatic HTLV-1 carriers (426 males and 792 females) who were enrolled during 2002–2008 for a prospective study on the development of ATL [15]. The HTLV-1 proviral load at enrollment was significantly higher in males than females (median, 2.10 vs. 1.39 copies/100 peripheral blood mononuclear cells (PBMC)) ($P < .0001$), in those aged 40 or more years, and in those with a family history of ATL. During the follow-up period, 14 participants developed ATL. Their baseline proviral loads were high (range, 4.17–28.58 copies/100 PBMC). Multivariate Cox regression analyses indicated that not only a higher proviral load but also advanced age, a family history of ATL, and the first opportunity for HTLV-1 testing during treatment for other diseases were independent risk factors for the progression of ATL from a carrier status.

Molecular features of HTLV-1 and ATL

The HTLV-I gene encodes three structural proteins, Gag, Pol and Env, and complex regulatory proteins such as Tax, which not only activates viral replication but also induces the expression of several cellular genes. The expression of the proteins encoded by these cellular genes may enhance the multistep carcinogenesis of ATL. However, the expression including Tax is suppressed in vivo probably

escaping from immune surveillance, and appears just after in vitro culture [10]. A new viral factor, HTLV-1 basic Zip factor (HBZ), encoded by minus strand mRNA was recently discovered and is thought to be involved in viral replication and T-cell proliferation [16]. Several isoforms of HBZ transcripts were reported to be steadily expressed in HTLV-1–infected cells and primary ATL cells in contrast to Tax. The functions of these transcripts and putative proteins in the context of cellular transformation are now under investigation.

Prototypical ATL cells have a mature helper T-cell phenotype (CD3+, CD4+, CD8−). Recent studies have suggested that the cells of some ATL patients may be the equivalent of regulatory T cells because of the high frequency of expression of CD25/CCR4 and about half of that of FoxP3 [17]. By Southern blotting for both HTLV-1 integration and T-cell receptor (TCR) gene rearrangement, about 10–20% of ATL cases showed clonal changes during the transformation from indolent to aggressive disease [18]. Oligoclonal expansion of HTLV-1 infected pre-malignant cells was detected in asymptomatic HTLV-1 carriers by HTLV-1 integrated site-specific PCR [19]. Polycomb-mediated epigenetic silencing of miR-31 is implicated in the aberrant activation of NF-kB signaling in ATL cells [20]. A high rate of chromosomal abnormalities has been detected in HTLV-1-infected T-cell clones derived from HTLV-1 carriers [21]. Abnormalities in tumor suppressors such as p53 and p14/p16 are frequent and rare in acute- and chronic-type ATL, respectively, and both are associated with poor prognosis [22]. Chromosomal abnormalities detected by cytogenetics or comparative genomic hybridization are often more complex and more frequent in acute ATL than in chronic ATL, with aneuploidy and several hot spots such as 14q and 3p [23]. Microarray analyses of the transcriptomes of ATL cells at the chronic and acute stages elucidate the mechanism of stage progression in this disease revealed that several hundred genes were modulated in expression including those for MET, a receptor tyrosine kinase for hepatocyte growth factor and cell adhesion molecule, TSLC1 [24,25].

In summary, ATL is etiologically associated with HTLV-1. However, HTLV-1 does not carry a viral oncogenes, expression of the virus including Tax appears just after in vitro culture. Integration of the provirus into the host genome is random, and chromosomal/genetic abnormalities are complex: therefore, ATL is regarded as a single HTLV-1 disease entity with diverse molecular features resembling the acute-crisis-phase of chronic myeloid leukemia.

Clinical features and prognostic factors of ATL

ATL patients show a variety of clinical manifestations because of various complications of organ involvement by ATL cells, opportunistic infections and/or hypercalcemia [10,11,26]. These three often contribute to the extremely high mortality of the disease. Lymph node, liver, spleen and skin lesions are frequently observed. Although less frequently, digestive tract, lungs, central nervous system, bone and/or other organs may be involved [26]. Large nodules, plaques, ulcers, and erythrodermas are common skin lesions [27–29]. Immune suppression is common. Approximately 26% of 854 patients with ATL had active infections at diagnosis in a prior nationwide study in Japan [14]. The infections were bacterial in 43%, fungal in 31%, protozoal in 18%, and viral in 8% of patients. Individuals with indolent ATL might have no manifestation of the disease and are identified only by health check-ups and laboratory examinations.

ATL cells, so called "flower cells", are usually detected easily in the blood of affected individuals except in smoldering type, which mainly has skin manifestations and lymphoma type [11]. The histological analysis of aberrant cutaneous lesions or lymph nodes is essential for the diagnosis of the smoldering type with mainly skin manifestations and lymphoma type of ATL, respectively. Because ATL cells in the skin and lymph node can vary in size from small to large and in form from pleomorphic to anaplastic and Hodgkin-like cell with no specific histological pattern of involvement, distinguishing the disease from Sezary syndrome, other peripheral T-cell lymphomas and Hodgkin lymphoma can at times be difficult without examinations for HTLV-1 serotype/genotype [26].

Hypercalcemia is the most distinctive laboratory abnormality in ATL as compared to other lymphoid malignancies, and is observed in 31% of patients (50% in acute type, 17% in lymphoma type and 0% in the other two types) at onset [11]. Individuals with hypercalcemia do not usually have osteolytic bone lesions. Parathyroid hormone-related protein or receptor activator of nuclear factor kappa B ligand (RANKL) produced by ATL cells is considered the main factor causing hypercalcemia [30,31].

The diagnosis of typical ATL is not difficult and is based on clinical features, ATL cell morphology, mature helper-T-cell phenotype and anti-HTLV-1 antibody in most cases [11]. Those rare cases which might be difficult to diagnose can be shown to have the monoclonal integration of HTLV-1 proviral DNA in the malignant cells as determined by Southern blotting. However, its sensitivity is around 5% of ATL cells among normal cells. Furthermore, the monoclonal integration of HTLV-1 is also detected in some HAM/TSP patients and HTLV-1 carriers [32]. After the diagnosis of ATL, subtype-classification of the disease, reflecting prognostic factors, clinical features and natural history of the disease are based on the presence of organ involvement, leukemic manifestation and values for LDH and calcium, is necessary for the selection of appropriate treatment (Table 1) [11,33].

Major prognostic indicators for ATL, elucidated among 854 patients with ATL in Japan by multivariate analysis were advanced performance status, high LDH level, age of 40 years or more, more than three involved lesions, and hypercalcemia [34]. Additional factors associated with a poor prognosis include thrombocytopenia, eosinophilia, bone marrow involvement, a high interleukin (IL)-5 serum-level, CC chemokine receptor 4 (CCR4) expression, lung resistance-related protein (LRP), p53 mutation and p16 deletion by multivariate analysis [33]. Specific for the chronic type of ATL, high LDH, high blood urea nitrogen (BUN), and low albumin levels were identified as factors for a poor prognosis by multi-variate analysis [10]. Primary cutaneous tumoral type generally included among smoldering ATL had a poor prognosis in a uni-variate analysis [27].

Recently, a retrospective review of 807 patients in Japan led to a prognostic index for acute- and lymphoma-type ATL based on five prognostic factors; stage, performance status (PS), age, serum albumin and sIL2R. In the validation sample, the index was reproducible with median survival times (MSTs) of 3.6, 7.3, and 16.2 months for patients at high, intermediate, and low risk, respectively [35]. The Japan Clinical Oncology Group (JCOG)-Lymphoma Study Group (LSG) conducted a meta-analysis of three consecutive trials exclusively for aggressive ATL (see below) [36]. OS analysis of a total 276 patients with acute-, lymphoma- or unfavorable chronic-ATL identified two significant prognostic factors, PS and hypercalcemia. In the validation sample, a proposed prognostic index using the two factors into two strata revealed MSTs of 6.3, and 17.8 months for patients at high and low risk, respectively. In both

Table 1
Diagnostic criteria for clinical subtypes of adult T-Cell leukemia-lymphoma.

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte ($\times 10^3/\mu$UL)	<4	≥4	<4	[a]
Abnormal T lymphocytes	≥5%[d]	+[c]	≤1%	+[c]
Flower cells with T-cell marker	[b]	[b]	No	+
LDH	≤1.5 N	≤2 N	[a]	[a]
Corrected Ca^{2+} (mEq/L)	<5.5	<5.5	[a]	[a]
Histology-proven lymphadenopathy	No	[a]	+	[a]
Tumor lesion				
Skin and/or lung	[a]	[a]	[a]	[a]
Lymph node	No	[a]	Yes	[a]
Liver	No	[a]	[a]	[a]
Spleen	No	[a]	[a]	[a]
Central nervous system	No	[a]	[a]	[a]
Bone	No	No	[a]	[a]
Ascites	No	No	[a]	[a]
Pleural effusion	No	No	[a]	[a]
Gastrointestinal tract	No	No	[a]	[a]

HTLV-1, human T-lymphotropic virus type I; LDH, lactate dehydrogenase; N normal upper limit.
With permission from Shimoyama M, Members of the Lymphoma Study Group (1984–1987): Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991; 79:428.

[a] No essential qualification except terms required for other subtype(s).

[b] Typical "flower cells" may be seen occasionally.

[c] If the proportion of abnormal T lymphocytes is less than 5% in peripheral blood, a histologically proven tumor lesion is required.

[d] Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood.

studies, however, the 5-year OS rate was less than 15% even in the low risk group, indicating that they are not sufficient to properly identify non-candidates for allo-HSCT which can achieve a cure of ATL despite considerable treatment-related mortality.

Treatment of ATL

Current treatment options for ATL include watchful waiting until the disease progresses, interferon alpha (IFN) and zidovudine (AZT) therapy, multi-agent chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) and new agents.

Recently, a treatment strategy based on the clinical subtype classification and prognostic factors was suggested as shown in Table 2 [33].

Watchful waiting

At present, no standard management for indolent ATL exists. Therefore, patients with the smoldering or favorable chronic type, may survive one or more years without chemotherapy, excluding topical therapy for cutaneous lesions, are observed and therapy is delayed until disease progression [33]. However, it was recently found that the long-term prognosis of such patients was poorer than expected. In a long-term follow-up study for 78 patients with indolent ATL (favorable chronic- or smoldering-type) with a policy of watchful waiting until disease progression at a single institution in Japan, the MST was 5.3 years with no plateau in the survival curve. Twelve patients remained alive for >10 years, 32 progressed to acute ATL, and 51 died [37].

Chemotherapy

Since 1978, a number of consecutive chemotherapy trials have been conducted for patients newly diagnosed with ATL by the JCOG-Lymphoma Study Group (LSG) (Table 3) [10]. Between 1981 and 1983, JCOG conducted a phase III trial (JCOG8101) to evaluate LSG1-VEPA (vincristine, cyclophosphamide, prednisone, and doxorubicin) vs LSG2-VEPA-M (VEPA plus methotrexate (MTX)) for advanced non-Hodgkin lymphoma (NHL), including ATL [10]. The complete response (CR) rate of LSG2-VEPA-M for ATL (37%) was marginally higher than that of LSG1-VEPA (17%; $P = .09$). However,

Table 2
Strategy for the treatment of adult T-Cell leukemia-lymphoma.

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

Unfavorable chronic- or acute-type ATL
- 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 phase III trial against biweekly-CHOP) or AZT/IFN (evaluated by a meta-analysis on retrospective studies)
  - Poor prognostic factors: consider chemotherapy followed by conventional or reduced intensify allo-HSCT (evaluated by retrospective and prospective Japanese analyses, respectively).
  - Poor response to initial therapy: consider conventional or reduced intensity allo-HSCT

Lymphoma-type ATL
- If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP)
- Check prognostic factors (including clinical and molecular factors if possible) and response to chemotherapy:
  - Good prognostic factors and good response to initial therapy: consider chemotherapy followed by observation
  - Poor prognostic factors or poor response to initial therapy: consider chemotherapy followed by conventional or reduced intensity allo-HSCT.

Table 3
Results of sequential chemotherapeutic-trials of untreated patients with ATL (JCOG-LSG).

	J7801	J8101	J8701	J9109	J9303	JCOG9801	
	LSG1	LSG1/LSG2	LSG4	LSG11	LSG15	mLSG15/mLSG19	
Pts. no.	18	54	43	62	96	57	61
CR (%)	16.7	27.8	41.9	28.3	35.5	40.4	24.6
CR + PR (%)				51.6	80.6	72.0	65.6
MST (months)		7.5	8.0	7.4	13.0	12.7	10.9
2 yr. survival (%)				17.0	31.3		
3 yr. survival (%)				10.0	21.9	23.6	12.7
4 yr survival (%)		8.0	11.6				

CR: complete remission, PR: partial remission, MST: median survival time.

the CR rate was significantly lower for ATL than for B-cell NHL and peripheral T-cell lymphoma (PTCL) other than ATL ($P < .001$). The MST of the 54 patients with ATL was 6 months, and the estimated 4-year survival rate was 8%.

In 1987, JCOG initiated a multicenter phase II study (JCOG8701) of a multiagent combination chemotherapy (LSG4) for advanced aggressive NHL (including ATL). LSG4 consisted of three regimens: (1) VEPA-B (VEPA plus bleomycin), (2) M-FEPA (methotrexate, vindesine, cyclophosphamide, prednisone, and doxorubicin), and (3) VEPP-B, (vincristine, etoposide, procarbazine, prednisone, and bleomycin) [10]. The CR rate for ATL patients was improved from 28% (JCOG8101) to 43% (JCOG8701); however, the CR rate was significantly lower in ATL than in B-cell NHL and PTCL ($P < .01$). Patients with ATL still showed a poor prognosis, with an MST of 8 months and a 4-year survival rate of 12%.

The first phase II trial (JCOG9109) with a pentostatin, which was considered to be a promising agent showing responses against relapsed/refractory ATL as a single agent, -containing combination (LSG11) as the initial chemotherapy [38]. A total of 62 untreated patients with aggressive ATL (34 acute, 21 lymphoma, and 7 unfavorable chronic type) were enrolled. Among the 60 eligible patients, there were 17 CRs (28%) and 14 partial responses (PRs) (overall response rate [ORR] = 52%). The MST was 7.4 months, and the estimated 2-year survival rate was 17%. The prognosis of patients with ATL remained poor, even though they were treated with a pentostatin-containing combination chemotherapy.

In 1994, JCOG initiated a phase II trial (JCOG9303) of an eight-drug regimen (LSG15) consisting of vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin for untreated ATL [39]. Dose intensification was attempted with the prophylactic use of granulocyte colony-stimulating factor (G-CSF). In addition, non–cross-resistant agents such as ranimustine and carboplatin, and intrathecal prophylaxis with methotrexate and prednisone were incorporated. Ninety-six previously untreated patients with aggressive ATL were enrolled: 58 acute, 28 lymphoma, and 10 unfavorable chronic types. Approximately 81% of the 93 eligible patients responded (75/93), with 33 patients obtaining a CR (35%). The overall survival rate of the 93 patients at 2 years was estimated to be 31%, with an MST of 13 months. Grade 4 neutropenia and thrombocytopenia were observed in 65% and 53% of the patients, respectively, whereas grade 4 non-hematologic toxicity was observed in only one patient.

To confirm whether the LSG15 regimen would be considered as the new standard for the treatment of aggressive ATL, JCOG conducted a phase III trial comparing modified (m)-LSG15 (Fig. 1) with CHOP-14 (cyclophosphamide, hydroxy-doxorubicin, vincristine [Oncovin], and prednisone), both supported with G-CSF and intrathecal prophylaxis [37]. A total of 118 patients were enrolled. The CR rate was higher in the mLSG15 arm than in the CHOP-14 arm (40% vs. 25%, respectively; $P = .020$). The MST and OS rate at 3 years were 12.7 months and 24% in the mLSG15 arm and 10.9 months and 13% in the CHOP-14 arm {two-sided $P = .169$, and the hazard ratio was 0.75; 95% confidence interval (CI), 0.50 to 1.13}. In mLSG15 vs. CHOP-14, rates of grade 4 neutropenia, grade 4 thrombocytopenia and grade 3/4 infection were 98% vs. 83%, 74% vs. 17% and 32% vs. 15%, respectively. Three treatment-related deaths (TRDs), two from sepsis and one from interstitial pneumonitis related to neutropenia, were reported in the mLSG15 arm. The longer survival at 3 years and higher CR rate with mLSG15 compared with CHOP-14 suggest that mLSG15 is a more effective regimen at the expense of greater toxicity, providing the basis for future investigations in the treatment of ATL [40]. The superiority of VCAP-AMP-VECP in mLSG15 to

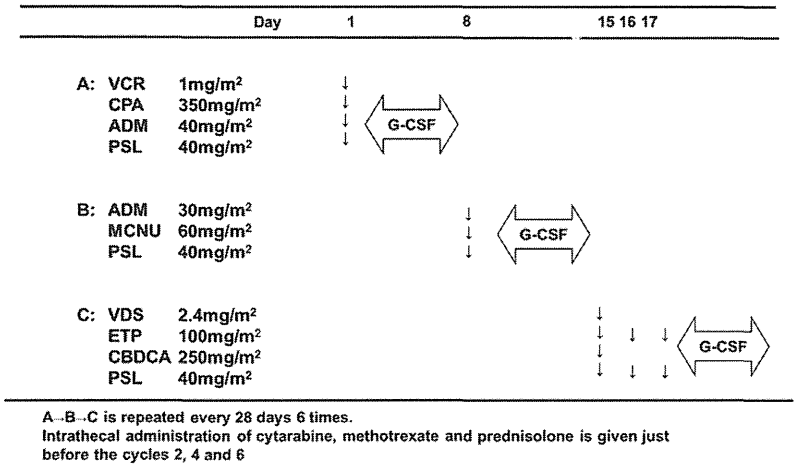

Fig. 1. Regimen of VCAP-AMP-VECP in mLSG15. VCAP = vincristine (VCR), cyclophosphamide (CPA), doxorubicin (ADM), prednisone (PSL); AMP = ADM, ranimustine (MCNU), PSL; VECP = vindesine (VDS), etoposide (ETP), carboplatin (CBDCA) and PSL. * MCNU and VDS are nitrosourea and vinca alkaloid, respectively, developed in Japan. A previous study on myeloma described that carmustine (BCNU), another nitrosourea, at 1 mg/kg is equivalent to MCNU at 0.8–1.0 mg/kg. VDS at 2.4 mg/m^2 can be substituted for VCR, another vinca alkaloid used in this regimen, at 1 mg/m^2 with possibly less myelosuppression and more peripheral neuropathy which can be managed by dose modification.

CHOP-14 may be explained by the more prolonged, dose dense schedule of therapy in addition to 4 more drugs. In addition, agents such as carboplatin and ranimustine not affected by multidrug-resistance (MDR)-related genes, which were frequently expressed in ATL cells at onset, were incorporated [10]. However, the MST of 13 months in VCAP-AMP-VECP (mLSG15) still compares unfavorably to other hematological malignancies, requiring further effort to improve the outcome.

Interferon-alpha and zidovudine

In 1995, Gill and associates reported that 11 of 19 patients with acute- or lymphoma-type ATL showed major responses (5 CR and 6 PR) to a combination of IFN and zidovudine (AZT) [41]. The efficacy of this combination was also observed by Hermine and associates; major objective responses were obtained in all five patients with ATL (four with acute type and one with smoldering type) [42]. Although these results are encouraging, the OS of previously untreated patients with ATL was relatively short (4.8 months) compared with the survival of those in the chemotherapy trials conducted by the JCOG-LSG (7–8 months) [43]. Since then, several small phase II studies using AZT and IFN have shown responses in ATL patients. The therapeutic effect of AZT and IFN is not a direct cytotoxic effect of these drugs on the leukemic cells. Enduring AZT treatment of ATL cell lines resulted in the inhibition of a telomerase, reprograming the cells to a p53-dependent senescence [44].

Recently, the results of a "meta-analysis" on the use of IFN and AZT for ATL were reported [45]. A total of 100 patients received interferon-alpha and AZT as initial treatments. The ORR was 66%, with a 43% CR rate. In this worldwide retrospective analysis, the MST was 24 months and the 5-year survival rate was 50% for first-line IFN and AZT, vs. 7 months and 20% for 84 patients who received first-line chemotherapy. The MST of patients with acute-type ATL treated with first-line IFN/AZT and chemotherapy was 12 and 9 months, respectively. Patients with lymphoma-type ATL did not benefit from this combination. In addition, first-line IFN/AZT therapy in chronic- and smoldering-type ATL resulted in a 100% survival rate at a median follow-up of 5 years. However, because of the retrospective nature of this meta-analysis based on medical records at each hospital, the decision process to select the therapeutic modality for each patient and the possibility of interference with OS by second-line treatment remains unknown. A prospective multicenter phase III study evaluating the efficacy of IFN/AZT as compared to watchful-waiting for indolent ATL is to be initiated in Japan.

Researchers from the UK reported the results of a retrospective analysis in 73 patients with aggressive ATL (acute ATL, 29; lymphoma ATL, 44) and suggested that chemotherapy with concurrent/

sequential IFN/AZT as initial treatment might improve survival for both the acute- and lymphoma-types of ATL compared with chemotherapy alone [46].

Recently, a phase II study of the combination of arsenic trioxide, IFN, and AZT for chronic ATL revealed an impressive response rate and moderate toxicity [47]. Although the results appeared promising, the addition of arsenic trioxide to IFN/AZT, which might be sufficient for the treatment of chronic ATL as described above, caused more toxicities and should be evaluated with caution.

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT)

Hishizawa and coworkers reported the results of a nationwide retrospective study in 386 patients with ATL who underwent allo-HSCT between 1996 and 2005 with several kinds of conditioning regimens [48]. The 3-year OS for the entire cohort was 33% (95% CI, 28%–38%). Multivariable analysis revealed 4 recipient factors for a poor prognosis: older age (>50 years), male sex, status other than CR, and use of unrelated cord blood compared with use of HLA-matched related grafts. Treatment-related mortality was higher among patients given cord blood transplants; disease-associated mortality was higher among male recipients or those given transplants not in remission. Among patients who received related transplants, donor HTLV-1 seropositivity adversely affected disease-associated mortality. Using the same cohort, it was recently found that the development of mild-to-moderate acute GVHD confers a lower risk of disease progression and a beneficial influence on survival among allografted patients with ATL [49].

In addition to conventional allo-HSCT, Okamura and associates reported the results of consecutive multicenter feasibility studies of reduced-intensity allo-HSCT against ATL [50]. Analysis of the combined data from both studies disclosed that grade I-II acute GVHD was the only factor that favorably affected OS and PFS and the long term prognosis after RIST was promising [51].

More recently, an expanded cohort of the above studies was analyzed for a comparison of myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) for allo-HSCT [52]. Although no significant difference in OS between MAC and RIC was observed, there was a trend indicating that RIC contributed to a better OS in older patients. Regarding mortality, RIC was significantly associated with ATL-related mortality compared to MAC.

The minimal residual disease after allo-HSCT detected as HTLV-1 proviral load was much less than that after chemotherapy or AZT/IFN therapy, suggesting the presence of a graft-versus-ATL effect as well as graft-versus-HTLV-1 activity [47].

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, sources of stem cells and HTLV-1 viral status of the donor, remain to be determined. Recently, a patient in whom ATL derived from donor cells developed four months after transplantation of stem cells from a sibling with HTLV-I was reported [53]. To evaluate the efficacy of allo-HSCT more accurately, especially in view of a comparison with intensive chemotherapy alone, a prospective multicenter phase II study of mLSG15 chemotherapy followed by allo-HSCT is ongoing (JCOG0907).

New agents for ATL

Purine analogs

Several purine analogs have been evaluated for ATL. Among them, pentostatin (deoxycoformycin) has been most extensively evaluated as a single agent and in combination as described above [38].

Other purine analogs clinically studied for ATL are fludarabine and cladribine. Fludarabine is a standard treatment for B-cell chronic lymphocytic leukemia and other lymphoid malignancies. In a phase I study of fludarabine in Japan in which 5 ATL patients and 10 B-CLL patients with refractory or relapsed-disease were enrolled [54], 6 grade 3 non-hematological toxic events were observed among the ATL patients. A PR was achieved only in one of the 5 ATL patients and the duration was short. Cladribine is among the standard treatments for hairy cell leukemia and other lymphoid malignancies. A phase II study of cladribine for relapsed/refractory aggressive-ATL in 15 patients revealed only one PR [55].