10年，15年での全生存割合と無急性転化生存割合がそれぞれ，47，25，14%と46，21，8%であり，生存曲線にプラトーはなく，長期予後は良好ではなかった[18]。一方，昨年の海外からの後方視的報告で17例のくすぶり型または慢性型のIFN/AZT療法の成績では，観察期間中央値約5年で，生存割合は100%と有望であったことから，JCOG-PC908試験が計画された[15]。

本研究では，未治療のindolent ATL患者を対象として，IFN/AZT療法が，標準治療であるWW療法よりも有用であるか否かを検証するため，ランダム化第III相試験を行う。主評価項目は無イベント（急性転化）生存期間，副次評価項目は全奏効割合である。本試験ではwatchful waiting群の2年無イベント生存割合を60%と仮定し，IFN/AZT療法はこれに20%上回る必要があるとした。有意水準片側5%，検出力70%，登録期間3年，追跡期間2年とし，両群合わせて74例を予定症例数とした。さらには附随研究として，分子異常について患者血液検体を解析し，治療反応性と予後を予測するバイオマーカーを解明することも計画している。

本臨床試験は，平成20年に設けられた高度医療評価制度によって，現在ATLに対して保険適用のないIFNαとAZTを用いる。現在，高度医療評価会議及び先進医療専門家会議での審査・承認前の段階である。試験結果がよく標準治療の確立というエビデンスを創出できれば，企業，学会，患者団体に働きかけてATLに対するIFNとAZTの薬事法上の適応拡大の承認，保険適用（効能追加）を目指している。

2）Aggressive ATLに対する臨床試験

Aggressive ATLに対する標準治療としては，日本では強力な化学療法単独またはそれに引き続いてのAllo-HSCT，海外ではそれに加えてリンパ腫型以外ではIFN/AZT療法があげられている（表1）[16]。

aggressive ATLに対する有効な治療法の確立を目指し，JCOGリンパ腫グループは多剤併用化学療法の臨床試験を1970年代より継続して行ってきた[13]。ともにG-CSFを併用し強度を上げたCHOP-14療法とVCAP-AMP-VECP療法との第III相試験JCOG9801では，毒性は強かったが完全奏効割合と生存割合が上回っていた後者を標準治療として確立した。しかし生存期間の中央値は約13か月と他の造血器悪性腫瘍と比べて依然極めて不良であり，化学療法のみの治療戦略には限界があると考えられている[19]。

近年，同種造血幹細胞移植療法（allo-HSCT）は，有害反応は強いが宿主片対ATL効果により長期生存が期待できるとの報告が，主に日本から相次いでいる[20~23]。Allo-HSCTでは，移植前処置の強度，ドナー，幹細胞のソースなどヴァリエーションがあり，特にATLは比較的高齢者に多いことから骨髄破壊的な前処置か非破壊的な前処置などの工夫が重要である。

厚生労働省がん臨床研究班の岡村班，鵜池班では継続的に，比較的高齢者のAggressive ATLに対する骨髄非破壊的allo-HSCT（NST）のFeasibility StudyをウイルスCorrelative studyとともに行ってきた。その初期の試験結果から，NSTが比較的安全に高齢者ATLに

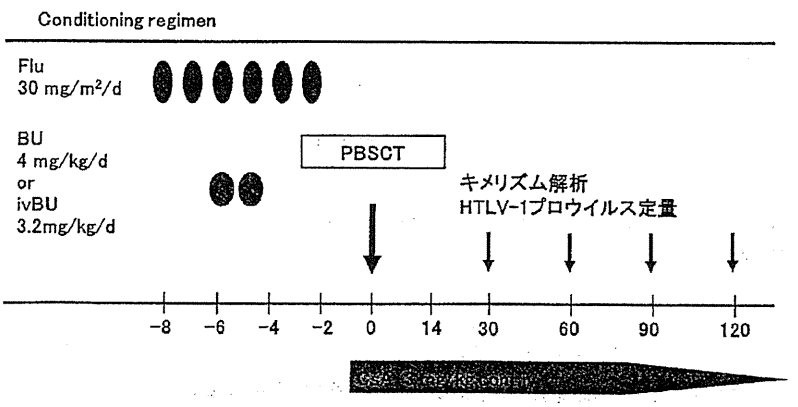
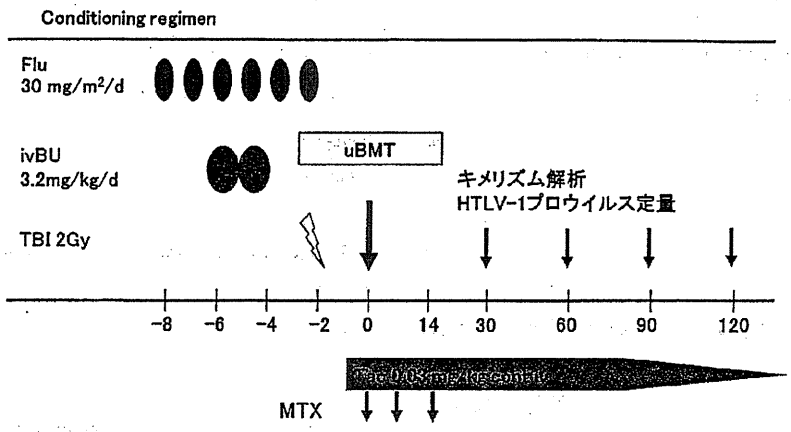


図2 成人T細胞白血病リンパ腫（ATL）に対する同種末梢血幹細胞による骨髄非破壊的移植療法の検討：多施設共同第II相試験（ATL-NST-3）



目的：急性型あるいはリンパ腫型の成人T細胞白血病リンパ腫症例に対して、骨髄非破壊的前処置を用いた非血縁者間骨髄移植の安全性を検討する。
対象：急性型あるいはリンパ腫型ATL患者で、化学療法などによって、病状がCRまたはPR以上にコントロールされている症例で、適切な血縁ドナーを有さない症例(50～65歳または49歳以下で規定の臓器障害あり)。
主要評価項目：移植後100日時点での生存かつ100日以内の完全キメラ達成
予定症例数と集積期間：15例、2年間

図3 成人T細胞白血病リンパ腫（ATL）に対する非血縁者間同種骨髄移植における骨髄非破壊的処置療法の安全性を検討する第Ⅰ相試験（ATL-NST-4）

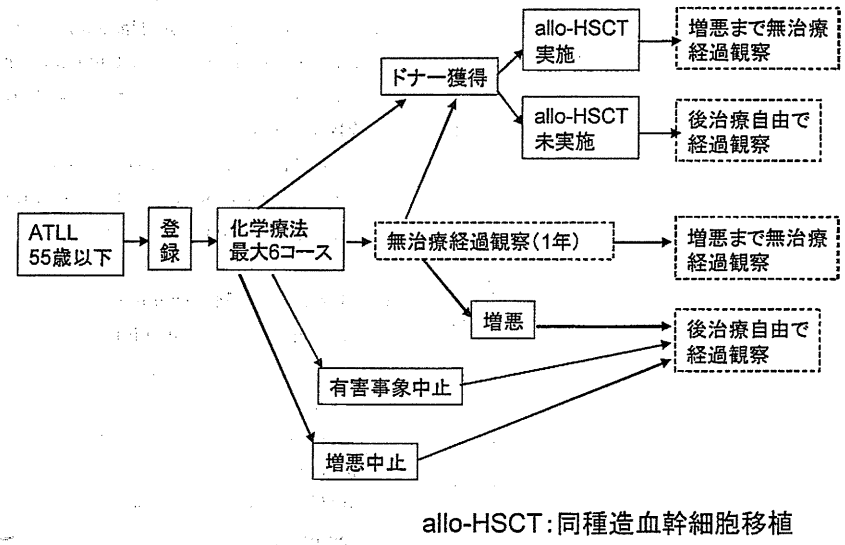


図4 成人T細胞白血病・リンパ腫に対する骨髄破壊的前処置法を用いた同種造血幹細胞移植療法を組み込んだ治療に関する第Ⅱ相試験（JCOG0907）

できること，GVHDを伴うと再発が少ないこと，移植後にはCTL活性が出現し，ウイルス量が減じることを報告してきた[21,22,24]。それを受けて現在は図2，3に示す2つの臨床試験が進行中である。

ATLに対するallo-HSCTについての検証的な臨床試験は，対象となる患者数が限られているため容易ではない。図4に示すJCOG0907試験では，本疾患に対するallo-HSCTがその高いリスクに見合う治療法であるか否かを検証するために，20歳以上55歳以下の初発Aggressive ATL患者を対象として，導入化学療法（VCAP-AMP-VECP）を開始した後，ドナーが確保された場合に骨髄破壊的な前処置法を用いたallo-HSCTを施行する。この一連の治療の有効性と安全性をヒストリカルコントロールである化学療法と比較する非ランダム化検証的試験である。主要評価項目は3年全生存割合，予定症例数130名，登録期間5年を予定している。

ATL患者の臨床研究への参加促進について

別稿の内丸薫先生の総説にあるように，多発国である日本においてもその希少性／偏在性のために，他の造血器腫瘍と比べて地域によってATLの治療方針には差異が大きい。前述したように，昨年度から始まったHTLV-1総合対策の一環として，ATLに対する臨床試験を推進する体制が構築されつつある。HTLV-1キャリア，ATL，HTLV-1関連性脊髄症（HAM）患者の方々からの要望では，これまで他のウイルス関連疾患とくらべて不十分であったHTLV-1対策の中でも，致死的な疾患であるATLの治療法開発は重点項目の1つとしてあげられた。この状況を改善するための情報提供として最近以下の2つのウェブサイトが立ち上がった。1つは厚生労働省HPのHTLV-1（ヒトT細胞白血病ウイルス）に関する情報（http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou29/）であり，妊婦，キャリア，家族，医療関係者，支援者，自治体担当者を対象にして相談・医療機関検索，マニュアル・手引き，関係通知，リンク等を公開している。もう1つはATL/HAMについてのHTLV-1研究班合同委員会によるHTLV-1情報サービス（http://htlv1joho.org/index.html）であり，最新のHTLV-1に関連する専門的な情報を一元的に発信するとともに，患者・患者家族等が参考となる医療機関情報，臨床研究情報についても掲載し，適切な医療機関に円滑に結びつけることを目的として，HTLV-1関連疾患の説明，検査等の説明，用語解説，医療機関情報，臨床研究情報等を公開している。

また今年2月には厚生労働省がん臨床研究事業のATL臨床試験研究班合同で「ATL患者の臨床研究参加促進を図るためのリクルートシステムの開発」についての会議が開催され，上述したATLに対する臨床試験，さらには新薬の開発の推進について協議し，患者リクルートのための基盤を作った。また内丸薫先生の稿にあるように，これらの班の協同で全国のがん拠点病院，血液内科または皮膚悪性腫瘍の専門医がいる病院へATL診療の実態と意識調査を行い，その結果をATL患者の臨床研究参加促進へつなげるために解析した。

最 後 に

造血器腫瘍の中でも難治性であるATLに対する治療法の開発には，基礎・橋渡し研究，そして引き続いての臨床試験が重要である。現在ATLを含むT細胞腫瘍に対しては，臨床試験に進む直前の新薬，新規治療法が少なからずあり，期待されている。

ATL患者，HTLV-1キャリアの方々が望んでいるより良い標準的治療法の開発には，初発患者に対する集学的治療法と再発・難治患者に対する新薬，新規治療法の臨床試験が必須である。昨年度から強化されつつある患者参加促進の体制作りによって，ATLに対する臨床試験の進捗ペースがアップし，より適切な治療法が早期にかつ継続的に提供されることを望む。

著者のCOI（conflicts of interest）開示：本論文発表内容に関連して特に申告なし

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特集 リンパ系腫瘍診療のresearch questions

くすぶり型・慢性型成人T細胞白血病リンパ腫に対する無治療経過観察は適切な選択か？*

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岩永正子***,****
塚崎邦弘***

Key Words：adult T-cell leukemia-lymphoma (ATL), indolent type, prognosis, treatment strategy

はじめに

成人T細胞白血病リンパ腫(adult T-cell leukemia-lymphoma；ATL)は，ヒトTリンパ球向性ウイルス1型(human T-cell lymphotropic virus type I；HTLV-1)が病因の成熟T細胞腫瘍である．臨床的に，抗HTLV-1抗体陽性者で，末梢血，リンパ節，皮膚，その他の臓器に細胞・組織学的に特徴的な核形態を有するT細胞腫瘍を認めればATLと診断される[1]．下山らは，1990年代初頭に全国ATL調査を行い，約800症例の臨床病態と予後因子解析結果をもとに，ATLを急性型，リンパ腫型，慢性型，くすぶり型の4つの病型に分類し，それぞれの4年生存率(最長7年の追跡期間)は，5.0%，5.7%，26.9%，62.8%，生存期間中央値(median survival time；MST)は6か月，10か月，24か月，未到達，と，慢性型・くすぶり型は，急性型・リンパ腫型に比較して予後良好であると報告した(図1)[2]．しかし，最近ブラジルから，ATL患者70例の追跡結果(最長14年の追跡期間)が報告され，慢性型とくすぶり型ATLのMSTは，それぞれ18か月と58か月，全生存率は20%以下[3]と，下山らの報告より予後不良であった．さらに，石塚らによる26例のくすぶり型ATLの予後調査(最長15年の追跡期間)では，42%(11例)が急性転化したと報告されている[4]．最近われわれも，90症例の慢性型・くすぶり型ATLの長期追跡解析(最長17.6年の追跡期間)を行い，これらの病型は予想以上に不良であることを報告した[5]．本稿では，われわれの慢性型・くすぶり型ATLの長期追跡知見を紹介し，現時点における，

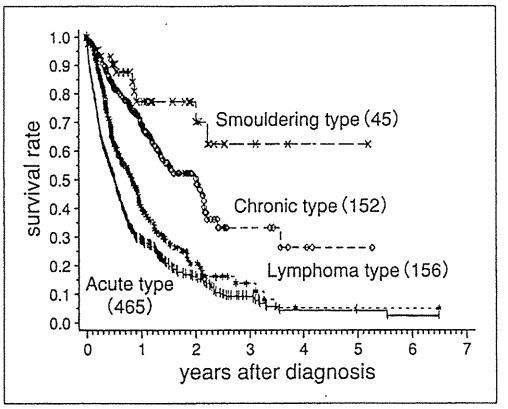

図1 日本におけるATL患者の下山分類による生存曲線：1990年代の報告
Smouldering type：くすぶり型，Chronic type：慢性型，Lymphoma type：リンパ腫型，Acute type：急性型．
(文献[2]より引用改変)

* Is management with watch-and-wait strategy always the appropriate choice for smoldering-or chronic-type adult T-cell leukemia-lymphoma?

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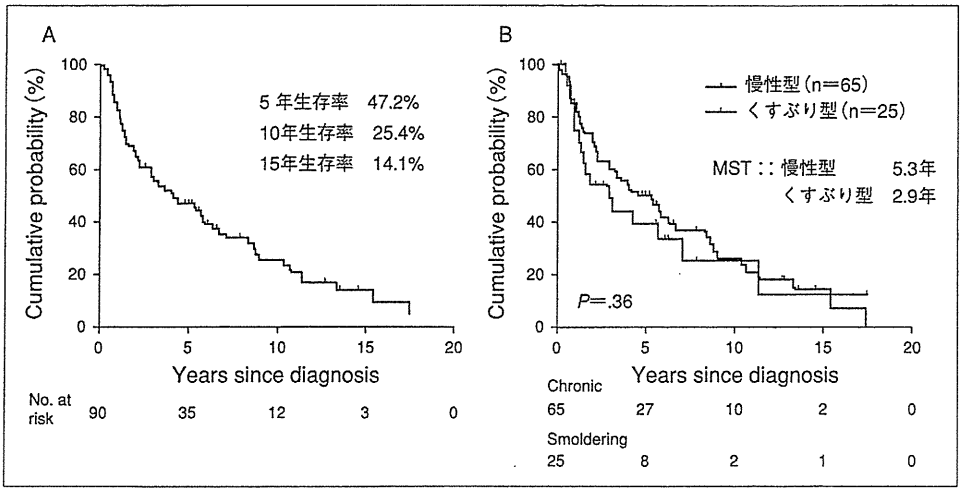

図２　全生存曲線(A)と亜型分類による生存曲線(B)（文献[5]より引用改変）

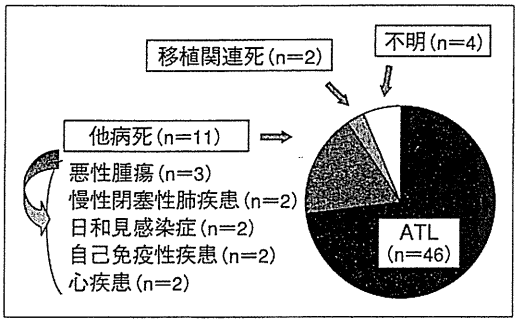

図３　死 因(文献[5]より引用改変)

これらの病型に対する国際的に推奨されている治療方針について解説する．

くすぶり型・慢性型ATLの長期予後

われわれは，1974年７月から2003年12月の間に，長崎大学を受診したくすぶり型ATL 25例と慢性型ATL 65例の計90症例を対象として，予後と予後因子を解析した．考慮した予後因子は，性別，年齢，performance status(PS)，診断時合併症の有無，白血球数，リンパ球数，好中球数，好酸球数，慢性型の予後不良因子[6](高LDH血症，高BUN血症，低蛋白血症；３つの要因の１つでも存在すれば陽性)の有無，リンパ節病変数，節外病変数，総病変数，化学療法施行の有無，である．

追跡期間中(中央値4.1年，範囲８日～17.6年)，63例(70%)が死亡し，５年，10年，15年生存率はそれぞれ47.2%，25.4%，14.1%であった(図2-A)．この結果は，近年のブラジルからの報告[3]に類似し，下山らの報告[2]より予後不良であった．また，追跡期間中44例(49%)が急性転化し(急性転化までの期間の中央値18.8か月，範囲0.3～17.6年)，うち41例が死亡した．死因の内訳は，急性転化後のATL死(41例)，ATL病状コントロール不良(慢性型の５例)，ATL以外の悪性疾患(３例)のほか，造血幹細胞移植関連死，慢性閉塞性肺疾患，日和見感染症，自己免疫性疾患，心疾患による死亡がそれぞれ２例ずつであった(図3)．つまり，急性転化による死亡の割合が最も多かった．

亜型分類別に予後をみると，くすぶり型25例のうち17例(68%)が死亡し，15年生存率は12.7%(生存期間の中央値2.9年)，うち15例が急性転化し死亡した．慢性型65例のうち46例(71%)が死亡し，15年生存率は14.7%(生存期間の中央値5.3年)，うち29例が急性転化して死亡し，５例は慢性型の病状コントロール不能で死亡した．しかし，くすぶり型と慢性型で生存率に有意差を認めなかった(図2-B)．

単変量の予後因子解析では，PS不良(２以上)，好中球増多，高LDH血症，PPS合併例，節外病変３領域以上，診断後の速やかな化学療法施行，が予後不良因子として同定されたが，多変量解析では化学療法施行のみが予後不良因子であった(図4，表1)．

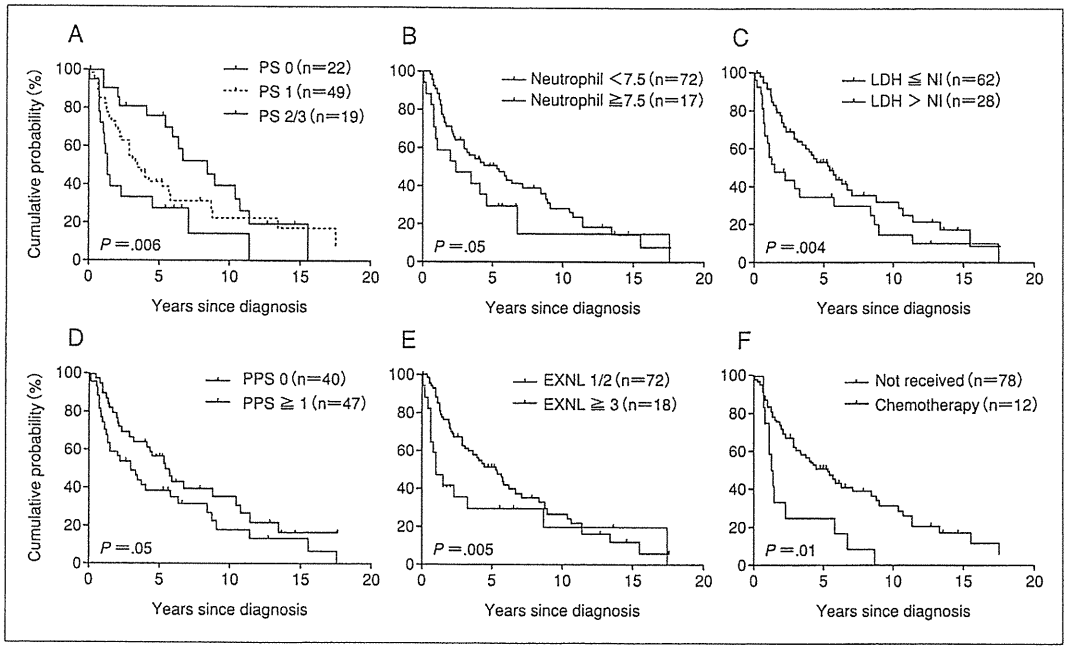

図4　臨床学的因子による生存曲線

A：PS，B：Neutrophil(好中球数)，C：LDH，D：PPS(予後不良因子)，E：EXNL(節外病変数)，F：化学療法施行の有無．　(文献[5]より引用改変)

表1　臨床学的因子

臨床的因子	全患者数(n=90)		
	単変量解析 HR(95% CI)	多変量解析A HR(95% CI)	多変量解析B HR(95% CI)
Performance status(PS)			
0	1	1	1
1	1.5(0.8～2.7)	1.4(0.8～2.8)	1.3(0.7～2.6)
≧2	2.5(1.2～5.2)	2.1(1.0～4.6)	2.1(1.0～4.6)
好中球数			
$<7.5\times10^9/l$	1	1	1
$\geqq7.5\times10^9/l$	1.6(0.9～2.9)	1.3(0.6～2.7)	1.2(0.6～2.3)
LDH			
基準値以内	1	1	1
基準値以上	1.7(1.0～2.9)	1.5(0.8～2.7)	1.5(0.8～2.6)
節外病変数			
0～2	1	1	−
≧3	1.5(0.8～2.8)	0.7(0.3～1.6)	−
総病変数			
1	1	−	1
2, 3	1.2(0.7～2.2)	−	0.8(0.4～1.6)
≧4	1.5(0.7～3.0)	−	0.9(0.4～2.1)
化学療法施行の有無			
化学療法未施行	1	1	1
化学療法施行	2.6(1.4～5.1)	2.3(1.1～4.7)	2.0(1.0～4.2)

HR：hazard ratio, CI：confidence interval, 多変量解析A：総病変数を除いた解析，多変量解析B：節外病変を除いた解析．　(文献[5]より引用改変)

われわれの症例の多くは，病状が急性転化するまで慎重に無治療経過観察されていたが，慢性型の12例は，慢性型診断後ただちに化学療法が施行された．治療の理由は，高LDH血症(8例)，重篤な骨髄浸潤(2例)，重篤な皮膚病変(2例)があったためである．化学療法の内容は，VCAP(vincristine, cyclophosphamide, doxorubicin, prednisone)-AMP(doxorubicin, ranimustine, prednisone)-VECP(vindesine, etoposide, carboplatin, prednisone) 2例，CHOP(vincristine, cyclophosphamide, doxorubicin, prednisone) 2例，CHOP類似2例，VEPA(vindesine, etoposide, prednisone, doxorubicin) 1例，etoposide経口療法1例であった．治療施行された12例すべてが死亡し(MST：1.4年)，治療未施行群と比較し予後不良であった．

くすぶり型，慢性型ATLに対する治療

以前から日本では，基本的に，ATLを低悪性度群(くすぶり型，予後不良因子を有さない慢性型)と高悪性度群(急性型，リンパ腫型，予後不良因子を有する慢性型)に分けて治療方針を決定してきた．ATLに対する臨床治験は，Japan Clinical Oncology Group Lymphoma Study Group(JCOG-LSG)において継続的に実施されてきたが[7][8]，化学療法，造血幹細胞移植療法の適格対象は高悪性度群に限定されている．実地医療では低悪性度の場合には無治療経過観察が多く，高悪性度の場合は強力な併用化学療法または同種造血幹細胞移植が用いられることが多かった．

急性型，リンパ腫型のATLに対して骨髄破壊的[9][10]，非破壊的同種造血幹細胞移植[10][11]の有用性については多くの報告がある．JCOGでは20歳以上55歳以下の急性型，リンパ腫型，予後不良因子を有する慢性型のATLの患者において，VCAP-AMP-VECP化学療法を施行しながら，ドナーの検索を行い骨髄破壊的な前処置を用いた同種造血幹細胞移植を積極的に施行する治療の有効性と安全性の検討の臨床試験が進行中である．JCOG以外では，ATLでPS不良がない70歳未満の症例では，治療決定予後不良因子の有無にかかわらず，初回治療としてVCAP-AMP-VECPを考慮し，それ以外の場合はQOLを重視し低用量のetoposide(ETO)やsobuzoxane(MST-16)を施行する場合もある[12]．しかしながらVCAP-AMP-VECPを施行しても2年生存率は30%程度[7][8]である．一方，ATL細胞のおよそ90%にCCR4(CC chemokine receptor 4)が発現し，CCR4発現は予後不良因子と考えられていることから[13]，再発した急性型ATL患者に対し抗CCR4抗体の第I相臨床試験が行われ，奏効率は30.8%であったと報告されている[14]．現在，VCAP-AMP-VECPに抗CCR4抗体を上乗せすることの有効性を検討する目的で，急性型，リンパ腫型，予後不良因子を有する慢性型のATLの患者にVCAP-AMP-VECP 4コースとVCAP-AMP-VECP 4コース終了後に抗CCR4抗体を併用する群のランダム化比較試験が進行している．

低悪性度ATLの場合は，症例によってさまざまな治療方法が行われてきた．低悪性度ATLで皮膚症状のみの場合は，従来から，ステロイド軟膏の局所療法，全身性のステロイド投与，etoposide(ETO)，sobuzoxane(MST-16)の内服投与，interferonや，psoralen plus ultraviolet A(PUVA)療法，外科的切除などの治療が行われてきた．また，低悪性度ATLで白血球増多が著明な場合(30,000/μl以上)，ETO, MST-16で白血球数をコントロールする場合があるが，慢性リンパ性白血病の場合と同様にその有用性はまだ検証されていない[12]．さらに，低悪性度ATLで日和見感染のある場合は，日和見感染の治療とともに化学治療を考慮する場合があるが，どの治療を選択するかは確立されていない．

一方，欧米では1995年以降，いくつかの小規模な第II相試験において，AZT/IFN-α併用療法[15][16]の有効性が報告されてきたが，多国籍多施設共同研究の後方視的解析においても，その有効性が確認されている[17]．彼らは，慢性型・くすぶり型におけるAZT/IFN-α 16例と化学療法6例を比較し，化学療法群の5年生存率が42%なのに対し，AZT/IFN-α群はすべてが5年生存しており，後方視的な解析であるが，AZT/IFN-αが有意であると結論づけている[17]．また，未治療の慢性型ATL 10例に対し，ヒ素/AZT/IFN-αの併用の第II相試験を行い，完全寛解例が7例で，皮膚病変の改善が著しく，HTLV-1 proviral loadも著明に低下し，ヒ素/AZT/IFN-αの併用療法も有望

表2　ATLの治療法についての推奨されたストラテジー

くすぶり型あるいは予後不良因子を有さない慢性型ATL
・前向き臨床試験への参加を考慮
・症候を有する患者(皮膚病変，日和見感染症ほか)：AZT/IFN-αまたはwatch and waitを考慮
・症候のない患者：watch and waitを考慮
予後不良因子を有する慢性型あるいは急性型ATL
・前向き臨床試験への参加を考慮
・臨床試験に参加しない場合，予後因子(臨床的因子と可能であれば分子生物学的因子)をチェック
＊予後良好群：化学療法(biweekly-CHOPとの第III相比較試験で評価されたVCAP-AMP-VECP) あるいは AZT/IFN-α(欧米伯の後方視的多施設調査により評価された)を考慮
＊予後不良群：化学療法に引き続いて骨髄破壊的，また非破壊的同種造血幹細胞移植療法(日本でのそれぞれ後方視的および前方視的解析で評価された)を考慮
＊初期治療の奏効が不十分：骨髄破壊的，また非破壊的同種造血幹細胞移植療法を考慮

＊リンパ腫型も同様の戦略をとる．ただし実態調査結果からはこの病型への有用性が低かったAZT/IFN-α療法は推奨されていない．　(文献[19]より引用改変)

と報告している[18]．しかしながら，日本ではATLに対するAZT/IFN-αの治療は承認されていない．

こういった状況の中，2009年，ATL診療に対する国際的コンセンサス(ガイドラインではない)がはじめて公表された(表2)[19]．急性型，リンパ腫型のATLに対して骨髄破壊的[9][10]，非破壊的同種造血幹細胞移植[10][11]の有用性について多くの報告があるため，治療決定予後不良因子を持つ高悪性度ATLの場合，初期治療の奏効が不十分な場合は造血幹細胞移植を考慮することが国際的コンセンサスでは推奨されている．予後不良因子(アルブミン，LDH，BUN異常のいずれか)を有する慢性型ATLの場合は，急性型と同様な治療を検討することがコンセンサスでは推奨されている．また，低悪性度ATLで症候を有する場合は，無治療経過観察かAZT/IFN-α療法を推奨している．これを受けて，無治療経過観察とAZT/IFN-α療法のどちらが有意に有効であるか検証するために，症候を有するくすぶり型と予後不良因子を有さない慢性型を対象に，ランダム化比較試験がJCOGで進行中である．

これまでに，治療選択にかかわる予後不良因子としては，高LDH値症，高Ca値症，PS不良，多臓器病変などの臨床的因子，interferon regulatory factor 4 発現異常，*p*53，*p*16ゲノム異常などが報告されている[19]．慢性型に限れば，高LDH値症，高Ca値症，PS不良のほかに，好中球増多[20]，chromosomal deletion genomic hybridization(CGH)法でのaneuploidyが1以上あること[21]も，予後不良因子として報告されている．コンセンサス会議ではp53の異常の重要性が指摘されたが，推奨すべきファクターとしては合意が得られなかった．

くすぶり型・慢性型ATLに対する治療の今後の課題

くすぶり型・慢性型ATLに対する治療においては，確立された治療法がない．無治療経過観察でいいのか，治療をすべきなのか？ の結論はでていない．さらに，治療するのであれば，診断時から治療した方がいいのか？ 治療開始の時期はいつなのか？ 治療法は何が第一選択なのか？ についても結論が出ていない．大規模な多施設臨床共同研究を行い，治療決定するための臨床的因子もしくは分子生物学的因子の確立，治療法の開発が望まれる．

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Drugs of Today 2011, 47(8): 615-623

CCC: 1699-3993/2011
DOI: 10.1358/dot.2011.47.8.1590785

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REVIEW

INTERFERON ALFA AND ANTIRETROVIRAL AGENTS: A TREATMENT OPTION FOR ADULT T-CELL LEUKEMIA/LYMPHOMA

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CONTENTS

SUMMARY

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by human T-cell lymphotropic virus type I, and its clinical subtypes are categorized into smoldering, chronic, lymphoma and acute types. The standard care for patients with the acute, lymphoma and unfavorable chronic types (aggressive ATL) consists of intensive chemotherapy with or without subsequent allogeneic hematopoietic stem cell transplant, or a combination of interferon alfa and an antiretroviral agent, while that for the chronic type without unfavorable prognostic factors and the smoldering type (indolent ATL) is watchful waiting. Recently, early intervention for indolent ATL employing interferon alfa and an antiretroviral agent has been reported to lead to a marked benefit in a retrospective study. This modality should be evaluated in larger clinical trials, since patients with indolent ATL show a median survival time of as short as 4-5 years.

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INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by human T-cell lymphotropic virus type I (HTLV-1). Clinical subtypes of ATL are categorized into smoldering, chronic, lymphoma and acute types based on prognostic factors such as serum levels of calcium and lactate dehydrogenase (LDH), and clinical features such as leukemic manifestations based on the retrospective analysis of the nationwide survey of ATL performed by the T- and B-cell Malignancy Study Group of Japan (1). The chronic type is further divided into favorable or unfavorable subgroups depending on the presence of three poor prognostic factors, namely, high LDH, high blood urea nitrogen and/or low albumin levels (2). The prognoses of acute and lymphoma type ATL and chronic type ATL with unfavorable prognostic factor(s) are extremely poor, and these are regarded as aggressive ATL. On the other hand, smoldering and chronic ATL with no unfavorable prognostic factor(s) have better prognoses than aggressive ATL, and are regarded as indolent ATL.

The recommended strategy for the treatment of ATL was proposed at the international consensus meeting held in 2007 (3). Chemotherapy for aggressive ATL and watchful waiting for indolent ATL comprise the standard of care in Japan, which is a major endemic area for ATL in the world. The Japan Clinical Oncology Group (JCOG) reported the results of a multi-institutional phase II study (JCOG9303) of sequential combination chemotherapy consisting of VCAP (vincristine, cyclophosphamide, doxorubicin and prednisone), AMP (doxorubicin, ranimustine and prednisone) and VECP (vindesine, etoposide, carboplatin and prednisone), in which the complete remission (CR) rate, median survival time (MST) and 2-year overall survival (OS) rate in 93 patients were 36%, 13 months and 31%, respectively (4). The results were similar in the subsequent phase III study (JCOG9801) randomizing patients to either modified VCAP–AMP–VECP or CHOP14 (cyclophosphamide, doxorubicin, vincristine and prednisone). The CR rate, MST and 3-year OS rate were 40%, 13 months and 24%, respectively, in the VCAP–AMP–VECP arm, and 25%, 11 months and 13%, respectively, in the biweekly CHOP14 arm (5). Based on this study, VCAP–AMP–VECP became a recommended regimen for aggressive ATL.

In addition to conventional chemotherapy, myeloablative allogeneic stem cell transplant (SCT) was applied for patients with aggressive ATL under the age of 55-60 years old, and achieved long-term survival in some (6, 7). A randomized phase III trial to determine the role of allogeneic SCT is ongoing as part of the JCOG studies. Moreover, reduced-intensity SCT (RIST) was applied especially for elderly patients with aggressive ATL, and showed safety and promising efficacy in a phase I trial conducted by the ATL-RIST study group in Japan (8-10). Consequently, the ATL-RIST study group is now conducting a phase II study.

The combination of interferon alfa (IFN) and an antiretroviral agent for patients with ATL is considered the standard of care around the world; however, this treatment approach has not been evaluated in Japan because neither agent has been approved for the treatment of ATL under national health insurance.

This article reviews the current status and future direction regarding IFN and antiretroviral treatment for ATL.

RESULTS WITH INTERFERON ALFA AND ANTIRETROVIRAL AGENTS FOR AGGRESSIVE ATL

This treatment approach was initially reported in 1995 by two independent groups in the United States and France (11, 12). Since zidovudine (AZT) is the most frequently used among antiretroviral agents for the treatment of ATL, this article will use the term IFN/AZT to represent combination treatment of IFN and any antiretroviral agents (Table I).

First, we summarize the key reports of IFN/AZT. Gill et al. reported 19 ATL patients, including 17 with the acute type and 2 with the lymphoma type, treated with recombinant IFN/AZT (11). Daily subcutaneous administration of 5 million units (MU) of interferon alfa, with dose escalation to 10 MU 1 week later if toxicity was acceptable, and oral administration of 1000 mg of AZT were administered to the patients. Both drugs were continued for at least 4 weeks after the achievement of CR, or for up to 1 year in the absence of CR. CR or partial remission (PR) was observed in 11 of 19 patients (58%), 7 of 12 previously untreated patients (58%) and 4 of 7 previously treated patients (57%). MST in CR or PR (CR/PR) patients was reported to be 13 months in all patients, 16 months in previously untreated patients and 18 months in previously treated patients. However, MST was as short as 3 months in all 19 patients, and 5 months in 12 previously untreated patients.

Hermine et al. reported their preliminary results in 3 patients (12), and again after expanding to 19 patients (13). In their study, a combination of recombinant IFN/AZT at daily doses of 9 MU and 1000 mg, respectively, was administered for a minimum of 2 months, with no

Table I. *Representative reports of interferon alfa/zidovudine for the treatment of adult T-cell leukemia/lymphoma.*

		Gill et al. (11)	Hermine et al. (13)	Matutes et al. (14)	White et al. (15)	Ramos et al. (16)
Previously untreated patients	CR/PR (%)	CR+PR 58	59/34	0/100	33/33	N.A.
	MST (months)	5	11	N.A.	N.A.	N.A.
	Subtype of ATL*	N.A.	11/2/0/0	2/1/0/0	3/0/0/0	N.A.
Previously untreated and treated patients	CR/PR (%)	26/32	53/24	0/67	6/11	23/18
	MST (months)	3	11	18	6	N.A.
	Subtype of ATL*	17/2/0/0	15/4/0/0	13/2/0/0	11/5/2/0	15/4/3/0

CR, complete remission; PR, partial remission; MST, median survival time; N.A., not available. *Acute/lymphoma/chronic/smoldering.

allowance of dose reduction for hematological toxicities for the first month. Responders received maintenance therapy for at least 1 year with 4.5 MU of IFN and 600 mg of AZT. CR and CR/PR among 17 evaluable patients were observed in 9 (53%) and 13 patients (76%), respectively, and those in previously untreated patients were as high at 59% and 92%, respectively. MST of previously untreated patients, previously treated patients and patients who achieved CR with this treatment was 11, 6 and 28 months, respectively.

Matutes et al. reported the outcome of 15 patients treated with IFN/AZT in clinical practice. Of these, 11 and 2 patients were diagnosed with acute and lymphoma type ATL, respectively; however, the exact diagnosis of the remaining 2 patients was unclear (14). At the start of IFN/AZT, four patients had progressive disease, eight were in PR or CR by previous treatment and the remaining three patients were treatment-naive with active disease. Recombinant IFN at a dose of 3-5 MU daily or every other day and AZT at a dose of 1000 mg were administered. The dose of IFN was escalated if it was considered to be well tolerated. Ten patients (67%), including 7 who had been previously treated, achieved PR, and the MST of 15 patients was 18 months, while that of patients who achieved PR was not reached after 4 years' observation.

White et al. reported the treatment results of 18 patients, including 9 with the acute type and 5 with the lymphoma type, crisis (transformation of smoldering or chronic to acute form) in 2 and chronic type in 2, treated with similarly planned dosing and schedule to Gill et al. (15). Their results showed that MST in the 18 patients was 6 months, and CR and PR were observed in 1 and 2 patients, respectively. These results may be inferior to those in other reports. One of the reasons suggested for the lower response rate was poor tolerability of patients to adequate doses due to myelotoxicities associated with heavy treatment before administering IFN/AZT.

Ramos et al. reported the results of IFN/AZT in 22 patients (15 with the acute type, 4 with lymphoma type and 3 with chronic type) who were evaluable for response among 28 patients enrolled in the study (16). They were treated with IFN (5-10 MU twice daily) and AZT (1500 mg twice daily) as induction. Patients who responded to induction therapy continued with 5 MU of IFN once or twice daily and 600 mg of AZT twice daily. For patients showing a prolonged clinical response, both drugs were tapered to be given as little as three times weekly at a dose of 3 MU of IFN and at a twice-daily dose of 300 mg of AZT as maintenance therapy. Five patients (23%; three acute and two unfavorable chronic type) entered CR, and four (18%) patients achieved PR. No patients with the lymphoma type responded to treatment. It is of note that IFN/AZT was considered to be a suppressive rather than curative regimen based on the fact that the persistence of low levels of T-cell clones was detected by polymerase chain reaction in the peripheral

blood obtained from long-term survivors in stable remission. Therefore, the investigators recommended the necessity for long-term maintenance therapy in patients who achieved remission.

Recently, we reported the treatment results involving three Japanese patients with refractory/relapsed aggressive ATL who were treated with IFN/AZT (17). It is difficult to draw any definitive conclusion from the results of only three patients, but IFN/AZT appeared to exhibit some anti-ATL effects to at least stabilize the disease rather than induce durable remission. One patient showed the complete disappearance of skin lesions infiltrated by ATL cells, and the elevation of soluble interleukin-2 receptor, a marker of the tumor burden, was under control during IFN/AZT treatment in two patients.

In general, most of the adverse events described in the above reports —neutropenia, anemia, thrombocytopenia, elevation of hepatic enzymes, infection, fever and fatigue— were manageable with supportive care, including administration of granulocyte colony-stimulating factor, transfusion of red blood cells and/or platelets.

Finally, Bazarbachi et al. reported the results of a meta-analysis on the use of IFN/AZT in ATL (18) (Table II). They performed a retrospective survey of therapeutic outcomes in patients treated at several institutes where IFN/AZT was routinely used for the treatment of ATL, and compared the OS between patients who received first-line IFN/AZT and those who received first-line conventional chemotherapy. Among the 254 reviewed patients, 231 patients had survival data available, and 207 patients received first-line treatment. First-line IFN/AZT was given to 45 of 98 acute type patients (46%). In contrast, only 15% (13/84) of patients with the lymphoma type received this combination. This difference in treatment selection between the acute and lymphoma types might be related to the fact that IFN/AZT has been reported to be less effective against lymphoma type ATL (19). In this study, MST in patients with acute type ATL treated with IFN/AZT and chemotherapy was 9 and 6 months, respectively, while that for lymphoma type ATL was 7 and 16 months, respectively. These results suggested that IFN/AZT would be more effective for the acute than lymphoma type, while the superiority of chemotherapy could be seen in the lymphoma type, in line with the former reports (19). Finally, the authors concluded that IFN/AZT should be considered the gold standard of first-line therapy for acute type ATL. However, there are several issues to take into consideration to assess the conclusions drawn from the results of retrospective studies (20). First, the patients included in their analysis were treated based on the local policy in each institute rather than on uniform criteria, and therefore, there are some possible biases in selecting two different therapeutic modalities, either IFN/AZT or chemotherapy. Second, it is difficult to compare the treatment results between patients treated practically and those enrolled in prospective clinical trials after con-

Table II. *Survival in adult T-cell leukemia/lymphoma.*

A. Retrospective study reported by Bazarbachi et al. (18)

	Acute		Lymphoma		Chronic and smoldering	
First-line treatment	IFN/AZT (n = 45)	Chemotherapy (n = 53)	IFN/AZT (n = 13)	Chemotherapy (n = 47)	IFN/AZT (n = 17)	Chemotherapy (n = 6)
MST (months)	9	6	7	16	N.R.	60
5-year OS	28%	10%	0%	18%	100%	42%

B. Japanese clinical trials and retrospective studies (4, 5, 22)

	Acute		Lymphoma		Chronic and smoldering
	Chemotherapy		Chemotherapy		Watchful waiting
First-line treatment	JCOG9303 (n = 56)	JCOG9801 (n = 39)	JCOG9303 (n = 27)	JCOG9801 (n = 12)	(n = 90)
MST (months)	11	13	20	14	49
3-year OS	N.A.	23%	N.A.	17%	47%

IFN/AZT, interferon alfa and zidovudine; MST, median survival time; OS, overall survival; N.R., not reached; N.A., not available.

firming the fulfillment of eligibility criteria; however, it should be noted that MST of the chemotherapy group and even that of IFN/AZT reported in their manuscript appeared to be worse than that reported in JCOG chemotherapy studies (4, 5).

In summary, it is very difficult to determine which treatment is superior between IFN/AZT and chemotherapy for aggressive ATL based on the currently available data reported by different study groups in different regions with unmatched patients' backgrounds.

INTERFERON ALFA AND ANTIRETROVIRAL AGENTS FOR INDOLENT ATL

There have been no extensive studies to elucidate the benefit of early intervention for patients with indolent ATL. A retrospective Japanese study failed to show the benefit of chemotherapy for chronic type ATL, in which MST was 7.4 years when employing watchful waiting (n = 90) and 2.0 years for patients treated with chemotherapy (n = 49) (21).

In a recent retrospective study reported by Bazarbachi et al., OS of smoldering and chronic type ATL patients was 100% beyond 5 years for IFN/AZT (n = 17) and 42% for chemotherapy (n = 6) (18). The results, of course, should be interpreted with caution, because the number of patients was small, the local treatment policy of each institute was used as initial management, and therefore, no criteria for selecting first-line chemotherapy or IFN/AZT have been disclosed, and, most importantly, patients who were observed by watchful waiting were not evaluated in the study (20). Takasaki et al. recently reported that the 5-year OS of patients with indolent ATL, who were mainly followed up by watchful waiting until disease progression, was as low as 47% (22). If one simply compares these two results, IFN/AZT seems to be a very promising candidate for the treatment of this cohort of patients.

Currently, there is no evidence supporting the benefit of medical intervention for indolent ATL except for the possible beneficial effects of IFN/AZT. Therefore, marked progress would be realized if the promising potential of IFN/AZT were to be confirmed in larger prospective studies for this type of ATL.

THE MECHANISM OF THE THERAPEUTIC EFFECT OF INTERFERON ALFA AND ANTIRETROVIRAL AGENTS FOR ATL

The mechanisms of the anti-ATL effects induced by IFN/AZT have not been defined. In fact, neither IFN nor AZT exhibits direct toxicity against ATL cell lines or fresh ATL cells obtained from patients who achieved CR after IFN/AZT therapy (23).

IFN has been used for hematological malignancies such as hairy cell leukemia, follicular lymphoma, cutaneous T-cell lymphoma, multiple myeloma and chronic myelogenous leukemia, as well as renal cell carcinoma and chronic hepatitis B and C. It is a cytokine with various biological effects, including the induction of certain enzymes, such as 2'-5'-oligoadenylate synthase and a protein kinase protein P1, suppression of cellular proliferation, immunomodulatory activities such as enhancement of the phagocytic activities of macrophages and augmentation of the specific cytotoxicity of lymphocytes to target cells, and inhibition of viral replication in virus-infected cells; however, its precise mechanism of action has not been well elucidated (24, 25). Telomerase activity is elevated in HTLV-1-infected cells (26-28). IFN reportedly triggers a rapid downregulation of human telomerase reverse transcriptase (hTERT) expression, followed by the suppression of telomerase activity in susceptible immortal hematopoietic cell lines, primary leukemic cells other than ATL, and normal T lymphocytes through the direct inhibitory effect of IFN on hTERT transcription (29).

Intracellular phosphorylation changes AZT to its active form, zidovudine triphosphate (ZDV-TP), which is incorporated into viral DNA and then reverse transcriptase is inhibited via DNA chain termination (30). ZDV-TP has been reported to be incorporated into cellular DNA in vitro, but the ability to inhibit cellular polymerases α and γ is 100-fold less potent than that for inhibiting HIV reverse transcriptase (30, 31). Therefore, ZDV-TP may not directly affect cellular DNA. Similar to IFN, AZT has been reported to inhibit telomerase activity at a concentration exhibiting little or no toxicity on cells, and thereby enhances toxicity induced by anticancer agents (32-37). The potential of AZT to inhibit telomerase activity resulting in progressive telomerase shortening, followed by the induction of cellular senescence with increased expression of the proapoptotic cell cycle regulator $p14^{ARF}$ (cyclin-dependent kinase inhibitor 2A, isoform 4), as well as activation and stabilization of p53 in HTLV-1-infected cell lines and ATL cells, was reported (38, 39). Of note, a study showed that tumor cells derived from 46 of 56 (82%) patients with acute or chronic type ATL had wild-type p53 (40).

AZT has not yet shown activity against HTLV-1 replication/expansion. Although AZT prevented HTLV-1 transmission when administered at the onset of infection in

vitro, anti-HTLV-1 activity on already infected cells has not been unequivocally established (41-44). The ability of antiretroviral agents including AZT to reduce the HTLV-1 virus load is modest in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis. This may be due to the fact that the major HTLV-1 replication takes place through the clonal expansion of infected cells rather than through the reverse transcriptase pathway (45, 46). In the absence of supportive evidence, antiretroviral agents probably do not induce a reduction of the HTLV-1 provirus load in ATL patients nor anti-ATL effects by a direct action as a reverse transcriptase inhibitor.

Sporadic reports indicate that AZT shows clinical activities against human cancers other than ATL, such as small non-cleaved cell lymphoma, in combination with interferon (47); non-Hodgkin's lymphoma in combination with methotrexate (48); oral Kaposi's sarcoma (49) and primary effusion lymphoma (50), which are related to acquired immunodeficiency syndrome; and post-transplant Epstein-Barr virus (EBV)-associated primary central nervous system lymphoma in combination with ganciclovir in a patient who was HIV-negative (51). Recovery of the immune function in HIV-infected individuals or the inhibition of nuclear factor NF-κB by AZT followed by the induction of apoptosis in EBV-positive Burkitt's lymphoma cell lines are a suggested mechanism of tumor suppression (52).

Recently, the molecular features of ATL cells related to sensitivity and resistance to IFN/AZT have been reported. Ramos et al. reported that the expression of nuclear c-Rel, which is an oncogenic subunit of NF-κB, and its putative target interferon regulatory factor 4 (IRF-4) in ATL cells is associated with resistance to IFN/AZT. Conversely, the lack of expression of both c-Rel and IRF-4 in tumor cells was associated with favorable responses to IFN/AZT such as CR and long-term survival. In their study, IRF-4 overexpression was observed in nearly all lymphoma type patients, and therefore, it was thought to be one of the reasons for the poor response to IFN/AZT in this type (16). Alizadeh et al. reported that IFN/AZT induced a marked upregulation of interferon response genes, whereas cell cycle-associated genes were silenced. Moreover, patients not responding to IFN/AZT failed to show the interferon response signature in a comparison of gene expression profiles in tumor cells before and immediately after IFN/AZT (53). Further study is needed to elucidate the molecular mechanisms of action and predictive factors regarding the response to IFN/AZT.

FUTURE DIRECTIONS

There are two distinct frameworks for the treatment of patients with aggressive ATL (3). One is a chemotherapy-based approach usually used in Japan, and we are now attempting to achieve long-term remission, or even cure, by incorporating first-line myeloablative or reduced-intensity allogeneic hematopoietic stem cell transplant (HSCT). The other is IFN/AZT-based therapy, which is frequently administered for acute type ATL patients outside Japan.

There are no definitive data indicating which treatment approach is favorable in clinical practice. This means that a prospective, randomized study is necessary to answer this question. Furthermore, extensive research is also required to elucidate the predicting factors' response to the two strategies by aiming at individualized treatment.

Watchful waiting is the Japanese standard of care for indolent ATL. We have recently recognized that the prognosis of this cohort is poorer than expected based on a previous report (1, 22). The JCOG Lymphoma Study Group is now planning a randomized phase III study which compares the outcome of IFN/AZT versus watchful waiting in patients with indolent ATL in Japan. This study can only answer the question of whether IFN/AZT really improves the prognosis of the cohort, and we hope to establish standard of care for patients with indolent ATL in the near future. Some risk factors for the progression of indolent to aggressive ATL, such as skin involvement or the number of white blood cells, have been suggested (54, 55). To maximize the benefit of IFN/AZT, which is of course more toxic and costly compared to watchful waiting, it is very important to stratify the risk factors for progression and elucidate factors predicting the response to IFN/AZT in patients with indolent ATL to clarify for whom and when the treatment should be performed. Furthermore, IFN/AZT with arsenic trioxide for chronic ATL might be an option in the future based on a phase II study (56).

In conclusion, we now have conventional chemotherapy using cytotoxic agents, IFN, antiviral agents, allogeneic HSCT and novel targeted agents (57, 58) for patients with ATL. It is time to conduct a prospective, randomized study to delineate indications for treatment modalities depending on the biology and clinical subtypes of ATL.

DISCLOSURES

The authors state no conflicts of interest.

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JJCO Japanese Journal of Clinical Oncology

Review Article: Study Group

Jpn J Clin Oncol 2012;42(2)85–95
doi:10.1093/jjco/hyr168
Advance Access Publication 6 December 2011

Lymphoma Study Group of JCOG

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Received August 8, 2011; accepted October 27, 2011

The Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) was initiated in 1978 by five institutions and now has 47 members. JCOG-LSG has focused on combined modalities, dose intensification and the incorporation of new agents for major disease entities of lymphoid malignancies. More than 30 trials including 10 randomized trials have been conducted for aggressive non-Hodgkin's lymphoma (NHL), adult T-cell leukemia–lymphoma (ATL), lymphoblastic lymphoma/acute lymphoblastic leukemia, Hodgkin's lymphoma (HL), multiple myeloma, NK/T-NHL and indolent B-NHL, and correlative epidemiological and pathological studies have been performed on human T-lymphotropic virus type-I and T/B cell phenotypes. The first trials for aggressive NHL revealed significant differences in the prognosis of ATL, non-ATL T-NHLs and B-NHLs, establishing a subclassification of ATL, and leading to the establishment of standard therapies for ATL and localized nasal natural killer/T-NHL. Recently, for B-NHLs including diffuse large B-cell lymphoma, mantle cell lymphoma, and indolent B-NHLs, regimens incorporating rituximab have been evaluated. The JCOG-LSG trials for HL led to the approval of dacarbazine for the National Health Insurance in Japan. The multicenter trials by the JCOG-LSG combining new modalities such as molecular-targeting agents will contribute to further improvements in the treatment of lymphoid malignancies.

Key words: clinical trial – lymphoid malignancy – Lymphoma Study Group – Japan Clinical Oncology Group – T- and B-cell lymphoma

INTRODUCTION

Lymphoid malignancies consist of B-cell and T/natural killer (NK)-cell neoplasms, which are clonal tumors of mature and immature B cells, T cells or NK cells at various stages of differentiation (1). Paradigm shifts in the management of lymphoid malignancies have been achieved by the discovery of new disease entities, revision of classifications and development of new agents. The diagnosis of lymphoid malignancies improved significantly in the 1980s mainly with the development of immunophenotypic analyses using monoclonal antibodies. This resulted in the discovery of several new disease entities. Among them, adult T-cell leukemia–lymphoma (ATL) was first described in Japan by Takatsuki and colleagues (2) in 1977 and was found to be associated with human T-lymphotropic virus type-I (HTLV-1), the first RNA retrovirus associated with human diseases, in the early 1980s (3–5).

Treatment of lymphoid malignancies has been improved by the development of standard combination chemotherapy such as CHOP, secondary in association with the advances in diagnosis and classification described above, and by the development of new agents and modalities such as an anti-CD20 antibody for CD20-expressing B cell