DOI: 10.2169/internalmedicine.46.0128

Figure 2. G-banded karyotype of lymphoma cells: 46,XX, -1, -1, -2, -3, add(4)(p14), del(7)(q34), -8, add(9)(p13), add(11)(p11), -14, -14, del(15)(q22), +mar1, +mar2, +mar3, +mar4, +mar5, +mar6, +mar7 [1], 47, idem, +mar [1], 46, idem, +8, -add(11), -mar7, +mar [2], 47, idem, -add(9), -13, +14, add(18)(q23), -mar7, +mar3 [1], 47, idem, -add(9), +add(9)(q34), +14, -16, add(18)(q23), -mar7, +2mar [1], 47, idem, -X, -add(9), +add(9)(q34), +14, add(18)(q23), -mar6, -mar7, +3mar [1], 46, XX [3]. Metaphases were G-banded by a trypsin-treated Giemsa stain. Abberant chromosomes are indicated by arrows.

a failure to destroy expression of the original L gene during a secondary light-chain rearrangement [receptor editing (3)] , 2) a clonal progression from a single rearranged light-chain into dual light-chain expressing cells, 3) simultaneous rearrangements at both light-chain loci. Among them, we speculated that a failure of receptor editing might underlie the generation of dual κ/λ positive clones in the present case, although the data available were too limited. In general, κ rearrangements are favored over λ rearrangements, and κ loci in λ producers are often rearranged and inactivated by rearrangements of the kappa-deletion element (KDE) (3, 4). However, it has also been reported that such processes occasionally fail to destroy the original κ light-chain gene (2, 3). Thus, it might be possible to consider that a moderately decreased germline band detected by Cκ probe (Fig. 1B-c) might imply the presence of rearrangement involving KDE to heptamer-nonamer recombination signal sequences, which causes the deletion of Cκ locus as well as Igκ enhancer (5). However, in the present case, this rearrangement might not be sufficient to inactivate the transcription of Igκ gene, thereby creating dual κ/λ light-chain positive clones. This point warrants further investigation.

Of interest is that the present case displayed a clinically aggressive course, whereas the previous case reports of κ/λ-dual expression in B-cell neoplasm were predominantly observed in indolent cases comprising CLL (2, 6-8). Unfortunately, there has been no evidence available demonstrating the biological properties of dual κ/λ producers, which would support our observations. In addition, we could not exclude the possibility that the clinical aggressiveness in the present case might be related to the underlying pathological features (aggressive B-cell lymphoma), and the coexistence of B-cell lymphoma-associated HPS, rather than dual κ/λ rearrangement/expression. Therefore, further investigations into similar cases would be necessary to clarify the molecular mechanism and the clinical significance of double light-chain producers.

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血液・腫瘍科，54(1)：56-62，2007

特集 血液腫瘍に対する国外大規模臨床試験の評価と国内診療へのインパクト

未治療進行期濾胞性リンパ腫に対する治療の現状*

石澤賢一**

Key Words：follicular lymphoma, advanced-stage, rituximab

はじめに

造血器腫瘍の中で，濾胞性リンパ腫(以下FL)はきわめて扱いにくい疾患である．われわれ臨床医は外来において，“がん”と宣告しながら治療方針は時として“経過観察”という，およそ一般社会通念(“早期発見，早期治療”)に反した診療行動をとらなければならず，通常その説明，同意取得には多大の時間が必要となる．

治療方針が決定して経過観察となっても自然退縮したり，あるいは逆に急速にリンパ節が腫脹する場合もある．また治療開始となって病変がすべて消失しても，すぐに再発することもあれば，逆に治療終了後病変が残存していても，無症状で長期間何事もなく経過することもある．まさにその臨床経過は“変幻自在”で，改めて“治療とは？”と深く考えさせられることの多い疾患である．

本稿では近年発表された未治療進行期FLに対するR-CHOP療法とCHOP療法の第III相試験の結果を中心に，進行期FLの治療の現状を概説する．

FLの臨床的な特徴

The non-Hodgkin's lymphoma classification projectは，WHO分類の前身となったILSC(International Lymphoma Study Group)分類に基づく各リンパ腫の臨床的な特徴の評価を行った[1]．これは8か国9施設より，1988年1月1日から1990年12月31日までの間の未治療非ホジキンリンパ腫症例を連続的に各200例収集し，病理診断とともに，臨床データを収集して，その臨床的な特徴を明らかにしたもので，合計1,403例が解析された．これによると，FLの頻度は22.1%(グレード1：9.5%，グレード2：6.2%，グレード3：6.4%)，男女比は男：女，42%：58%，年齢の中央値59歳，臨床病期I/II期の割合33%，骨髄浸潤陽性率42%，5年の全生存率72%，5年の治療成功生存率(failure free survival)40%であった．これらはFLが比較的高齢者に発症して，初発時に進行期が多く骨髄浸潤の頻度が高いこと，また5年後の生存者は70%を超えるが，その40%強は有病生存であり，治癒困難な疾患であることを示していた．

スタンフォード大学より，差しあたって治療が必要ない，つまり疾患の急速な進行が認められない無症状，高齢，合併症ありなどの条件を有する83人の進行期低悪性度リンパ腫症例(FL症例75%)に関して，当面無治療で経過観察とし，その後急激な病状の進行，全身症状の出現，血球減少が出現した場合，治療開始とした経過が報告された[2]．観察期間の中央値が50か月．5年，10年の生存率は82%，73%で，治療開始までの

* A present state of frontline therapy for untreated advanced-stage follicular lymphoma.

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表1 GELFの治療開始基準

- 7 cm以上の節性あるいは節外性の腫瘤
- 3個以上のリンパ節領域にそれぞれ3 cm以上の病変がある
- B症状がある
- 脾腫(下端が臍レベル以下)
- 圧迫症状(尿路系，眼窩，消化管)あるいは胸水，腹水の存在
- 白血化(腫瘍細胞＞5,000/μl)，血球減少(好中球＜1,000/μlあるいは血小板＜100,000/μl)

(文献[3]より引用改変)

中央値は3年であった．また23%に自然退縮が観察された．これを放射線療法，化学療法などのプロトコル治療が実施された131名と比較したところ，生存率は同等であった．また病理組織学的進展の頻度，時期の中央値は経過観察群で12%，57か月，プロトコル治療群で18%，54か月で頻度，時期ともに差はなかった．

進行期FLの治療

1. Rituximab導入前

FLの自然経過の検討より，rituximabの臨床導入前，進行期FLは当面経過観察を選択しても予後に影響を与えないと考えられたため，なんらかの症状，検査値異常が認められた時点で治療を開始するのが一般的であった．治療開始の目安として代表的なのがGELF(the Groupe d'Etude des Lymphomes Folliculaires)の基準である(表1)[3]．

しかし，治療早期開始の利益の有無を直接検証した大規模な臨床試験は行われていなかったため，BNLI(British National Lymphoma Investigation)は，当面経過観察で必要に応じて加療する“watch and wait”とchlorambuchil単剤との比較試験を実施した[4]．対象は18歳以上の無症状の進行期低悪性度リンパ腫．主要評価項目は全生存率(以下OS)，無増悪生存率(以下RFS)．試験デザインは，無作為化後chlorambuchil群はCR到達までchlorambuchil投与．CR後は3か月間のchlorambuchilの維持療法を実施し，治療効果が認められない場合，病気の進行が確認された場合はchlorambuchilを中止した．“watch and wait”群は，当面最長でも3か月間隔の頻度で経過観察して，B症状，疾患の急激な進行，重要臓器への浸潤などが確認された場合chlorambuchil群と同様の治療を開始するものであった．

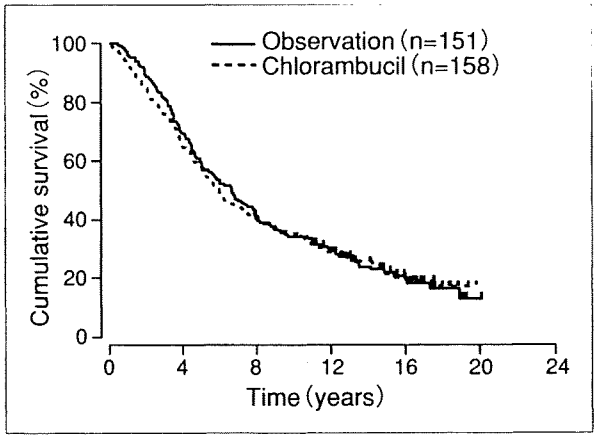

図1 OS(observation vs. chlorambucil)
(文献[4]より引用)

309名が登録され，chlorambuchil群に158名，“watch and wait”群に151名が割り付けられた．観察期間の中央値16年．5年，10年，15年のOSはchlorambuchil群で57%，35%，21%，“watch and wait”群で52%，34%，22%で，両群間に差を認めなかった(図1)．OS中央値もchlorambuchil群5.9年，“watch and wait”群6.7年で両群に差はなかった．さらに無作為化後10年の時点で，“watch and wait”群の19人が化学療法を受けずに生存していた(最終的な病理診断は，FL 6人，小リンパ球性リンパ腫7人，マージナルゾーンリンパ腫3人，分類不能1人，反応性2人)．FLは全体の66%であるが，経過観察期間が長期で，しかも追跡不能例が10年時点で1例，全経過でも3例と追跡の精度が高く，たとえ進行期であっても無症状で臓器機能障害をきたしていない場合は，既存の細胞障害性の化学療法の早期実施には利点がないことが明らかに示され，とくに70歳以上の症例に関しては“watch and wait”が推奨された．先のスタンフォード大学からのレポートが，前向きの臨床試験で証明された形となった．

またCALGBは，アルキル化剤単剤と併用化学療法との比較試験を実施した[5]．対象は未治療，診断より100日以内，臨床病期III/IVのFSCL(FL，グレード1相当)，FML(FL，グレード2相当)の患者である．アルキル化単剤群は，cyclophosphamide 100mg/m^{2}を血球数で用量を調節しなが

ら内服，併用化学療法群はCHOP-B療法6コースの後，CHOP療法をdoxorubicinの総投与量450mg/m²に達するまで継続し，CR, PR例に関しては，COP療法を4週間隔で実施された．両群ともに，最大の治療効果が得られてから2年間，治療を継続するデザインで実施された．

合計234名が登録され，解析対象となったのは228名(単剤群119名，併用療法群109名)である．10年時点での単剤群，併用療法群の治療不成功までの期間(以下TTF, time to treatment failure)，OSはそれぞれ25%対33%，44%対46%で有意差は認められなかった．したがって，FLの初回治療においては，治療強化の臨床的有用性は証明されなかった．

以上の結果をまとめると，rituximab導入前の進行期FLの初回治療に関して，“早期実施”，“治療強化”の臨床的メリットはなく，進行期FLの治療成績向上には，新たな機序の薬剤の臨床導入が不可欠であることが強く認識された．

2．Rituximab導入後

このような進行期FL治療の閉塞的な状況下で，注目されたのがrituximabである．再発低悪性度リンパ腫に対するrituximab単剤の治療成績は，奏効率48%，増悪までの期間(以下TTP)の中央値が13か月と，既存の抗がん剤とほぼ同等の治療効果を示し，毒性は軽度であった[6]．このrituximab単剤の臨床効果は，FLの予後を変えうるポテンシャルがあることが十分に予測され，また作用機序がユニークであったため，既存の化学療法との併用に関心が集まった．

低悪性度リンパ腫において前向き試験で，既存の細胞障害性の抗がん剤にrituximabを追加することの有効性を最初に検討したのはCzuczmanらが実施した第II相試験である[7]．対象はCD20陽性の既治療，未治療の低悪性度リンパ腫患者である．治療法はR-CHOP療法を6コース実施するものであるが，rituximabの投与時期が現在一般に行われているR-CHOP療法と異なり，rituximabのプライミング効果，相乗効果，微小残存病変根絶などを意図して，CHOP療法開始前に2回，CHOP療法2コース，4コース終了時にそれぞれ1回，6コース終了時に2回投与するものであった．主要評価項目は奏効率，副次的評価項目はTTPである．

40名(未治療31例，既治療9例)が登録され，評価可能症例38例．全奏効率100%(CR+CRu 87%)，TTP 82.3か月．PCR法によるbcl-2再構成の検出により微小残存病変評価可能であったのは8例である．その中の7例がPCR陰性になり，9年の経過観察後も3例は陰性を維持したままである．

未治療例と既治療例が混在していること，FLのみならず小リンパ球性リンパ腫も9例含まれていること，rituximabの投与スケジュールが現在一般的に実施されているものとは異なること，少数例の第II相試験であることなどを考慮しなければならない．しかしTTPの中央値が約7年で，かつ長期の分子生物学的寛解例も認められることより，rituximabの追加がFLの治療成績を改善する可能性があることを，はじめて前向きの臨床試験で示したものであった．

この結果を踏まえ，FLに対して一般臨床で広く実施されていたCVP療法と，CVP療法にrituximabを追加したR-CVP療法との比較試験が実施された[8]．

対象は18歳以上の未治療CD20陽性FL患者(グレード1, 2, 3)で，臨床病期III/IVで参加施設の担当医が，治療が必要と判断した症例である．CVP療法(day 1にCPA 750mg/m², VCR 1.4mg/m²で最大2 mg/body, day 1～5にPSL 40mg/m²)とR-CVP療法(CVP療法のday 1にrituximab 750mg/m²を加えたもの)に無作為に割付，21日間隔で最大8コース実施した．主要評価項目はTTFで，treatment failureとは病気の進行，再発・再燃，すべての理由の死亡，次治療の開始，4コース後に治療効果が認められないこと(CR, PRに到達しないこと)と定義された．

計322名が登録され，最終的にCVP群159名，R-CVP群162名が解析対象となった．追跡期間18か月時点での中間解析の結果で，最終解析実施が決定された．観察期間の中央値が30か月の時点で，TTFの中央値はCVP群が7か月，R-CVP群が27か月で，R-CVP群で有意に延長していた(P <0.0001)．また奏効率はCVP群57%(CR+CRu 11%)，R-CVP群81%(CR+CRu 41%)，奏効期間の中央値はCVP群14か月，R-CVP群35か月，次

治療開始までの期間もCVP群で中央値12か月，R-CVP群は中央値に達せず，主要評価項目のTTF以外でも，R-CVP群の優越性が示された．また毒性に関しては，グレード3,4の好中球減少がR-CVP群で24%，CVP群で14%であったが，感染症ならびに好中球減少時の敗血症の頻度は両群間で差がなかった．以上の結果より，CVP療法へのrituximabの追加は，問題となる毒性の増加なしに治療成績が改善すると結論づけられた(表2，図2)．

表2 CVP vs. R-CVP

	CVP療法	R-CVP療法	P値
評価可能症例	159例	162例	
奏効率	57%	81%	＜0.0001
CR＋CRu率	10%	41%	＜0.0001
TTP(中央値)	15か月	32か月	＜0.0001
TTF(中央値)	7か月	27か月	＜0.0001
奏効期間(中央値)	14か月	35か月	＜0.0001
OS(30か月)	85%	89%	＝0.22

(文献[8]より引用)

一方，CVP療法とともに一般臨床で未治療進行期FLに対して，広く実施されていたCHOP療法に対するrituximabの上乗せ効果を検証する第III相試験も実施された[9]．

対象は，18歳以上の未治療FLグレード1あるいは2の患者である．臨床病期III, IV期．かつB症状(盗汗，発熱，体重減少)，バルキー病変(最大径が縦隔で7.5cm以上，他の部位で5cm以上)，造血障害(ヘモグロビン10g/dl未満，好中球数1,500/μl未満あるいは血小板数10万/μl未満)あるいは急速な病状の進行のいずれかが認められることが適格条件とされた．治療スケジュールはランダム化後，CHOP療法群，R-CHOP療法ともに3週間隔で6～8コース実施された．4コース目までにCRに到達した場合は6コースで終了，それ以外は8コース実施し，CHOP療法あるいはR-CHOP療法終了後，60歳未満でCRあるいはPRに到達した場合，再度ランダム化してDexaBEAM療法後に，CY-TBIを前処置として自家移植，あるいはインターフェロンαの維持療法群を実施するものであった(図3)．主要評価項目はTTFで，treatment failureとは，治療抵抗性，原疾患の進行，死亡のいずれかが判明した場合と定義され，rituximabの上乗せにより，treatment failureの割合が50%減少すると仮定して，症例数が算定された．

2000年3月から2003年8月まで，630名が登録され，2003年6月の中間解析の結果，CHOP群と比較してR-CHOP群のTTPが有意に延長することが明らかとなり，2003年8月で登録は中止

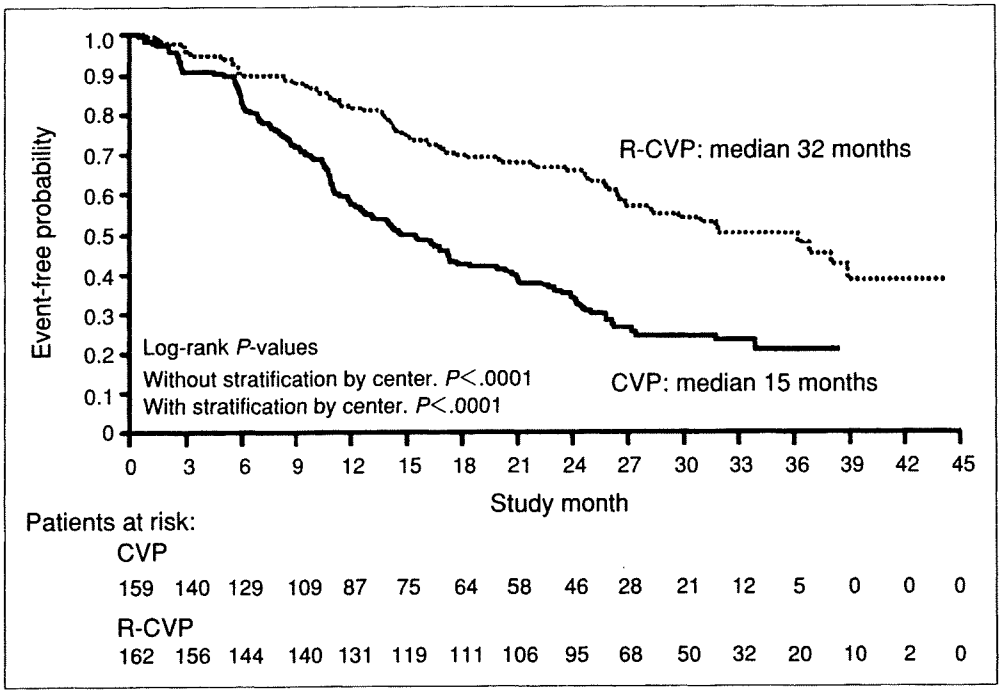

図2 TTP(R-CVP vs. CVP)(文献[8]より引用)

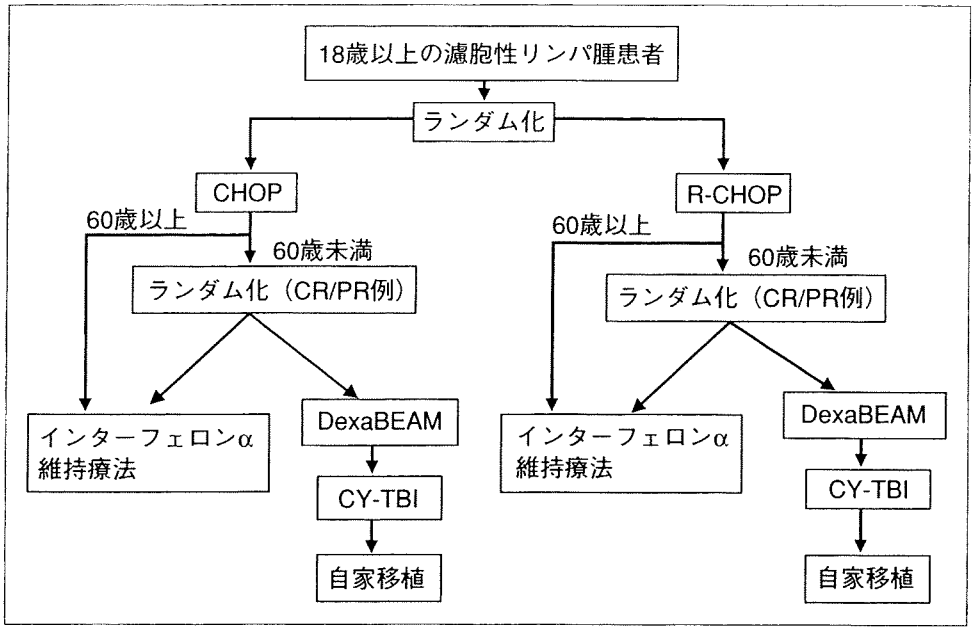

図3　GLSG試験のデザイン（文献[9]より引用）

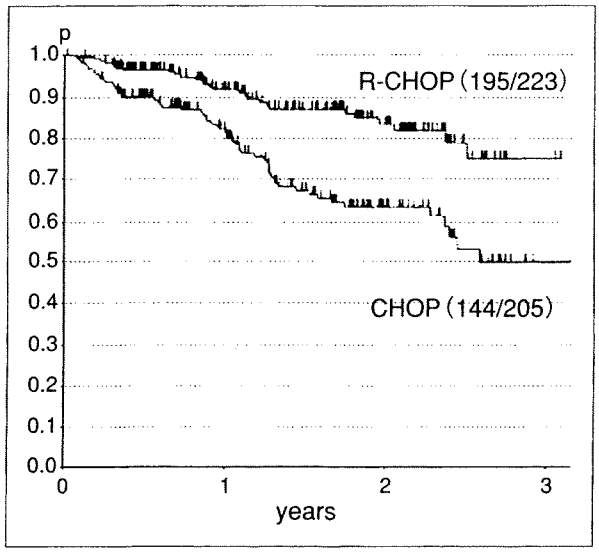

図4　TTF（R-CHOP vs. CHOP）（文献[9]より引用改変）

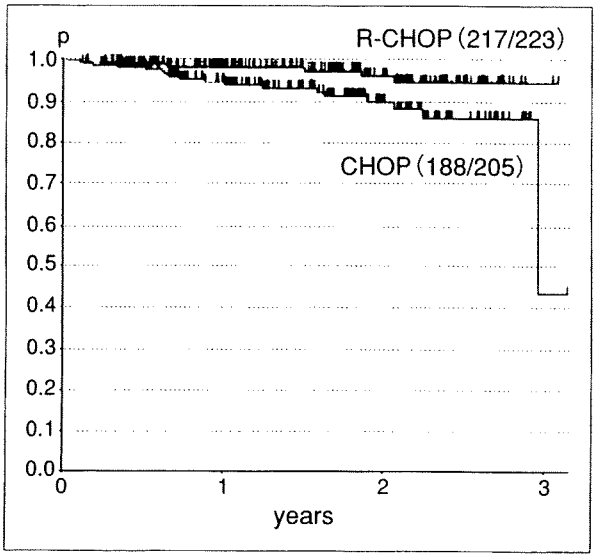

図5　OS（R-CHOP vs. CHOP）（文献[9]より引用改変）

となった．解析対象は，登録が中止になった時点で治療が終了していたCHOP群205人，R-CHOP群223人の計428名であり，R-CHOP群とCHOP群を比較して，奏効率（CR＋PR）はそれぞれ96%，90%（P=0.011），CR率は20%，17%（P=ns）であった．観察期間の中央値は18か月（範囲：1～38か月）でCHOP群と比較してR-CHOP群のtreatment failureのリスクは60%減少して，有意なTTFの延長が認められた（図4）．またFLでは，再発が次治療開始を意味しないため，無治療期間の評価も重要である．試験治療終了時より次治療開始までの期間，treatment-free intervalもR-CHOP群で有意に延長していた（P=0.001）．さらに観察期間が3年の時点で，死亡者数はR-CHOP群6名，CHOP群17名で，OSでもR-CHOP療法がCHOP療法を上回った（P=0.016）（図5，表3）．

表3　CHOP vs. R-CHOP

	CHOP療法	R-CHOP療法	P値
評価可能症例	205例	222例	
奏効率	90%	96%	0.011
CR率	17%	20%	ns
OS（2年）	90%	95%	0.016

ns：有意差なし　（文献[9]より引用）

60歳未満では維持療法について，大量化学療

法とインターフェロンαのランダム化を行っており，本来の目的であるCHOP療法とR-CHOP療法との直接比較がやや不明確になっているが，進行期FLの初回治療におけるrituximab追加の有用性を示したものといえる．

3．データベースの解析

SWOGでは過去にFLを対象として実施された臨床試験のPFS, OSの解析を実施した[10]．対象となった臨床試験は1974年から1983年に実施されたCHOP療法±免疫賦活療法356名，1988年から1994年まで実施されたProMACE-MOPP療法±インターフェロン療法425名，1998年から2000年まで実施されたCHOP療法→抗体療法(rituximabあるいは^{131}I-tositumomab)179名．4年時点でのCHOP療法→抗体療法のPFSは，それ以前の治療群と比較して13%から15%改善した．また4年のOSは，年代順に69%，79%，91%と有意に向上した．ProMACE-MOPP療法群のOSの改善は，二次治療における抗体療法の影響と推察され，初回治療における抗体療法の追加はFLの治療成績を向上させる可能性があると結論づけられた．

同様の報告は，2005年ルガノで開催された第9回悪性リンパ腫国際会議でもなされた．Horningはスタンフォード大学のFL症例の解析結果を示し，1995年以降に診断された症例のOSは1995年以前に診断された症例と比較して有意に向上していることを示し，その理由として，1995年以前の症例はほとんどrituximabの投与を受けていないこと，またワクチン療法の導入をあげた[11]．

これらの結果は，補助療法の進歩の影響も考慮しなければならないが，先に述べたrituximab併用化学療法の第III相試験の結果を裏づけるものであろう．

今後の進行期FL治療

以上より，FLの初回治療におけるrituximab追加の有用性に関しては，結論が出たと考えられる．

したがって今後はrituximabの併用を前提として，どのタイミングで，どのような状態の患者に，どのような化学療法を併用するのかが重要な検討課題となる．おそらくrituximabの毒性が軽度であること，腫瘍量が多い場合は効果不十分であることを考慮すると，治療開始のタイミングは早まるであろうし[12]，最適な併用化学療法も一律ではなく，FLIPIのスコアに応じて，あるいは腫瘍量に応じて変わるかもしれない．現在JCOGでは，rituximab併用下で，通常のCHOP療法とbiweeklyCHOP療法の比較試験が進行中である．また，プリン誘導体であるfludarabine[13]，cladribineを中心とした併用化学療法の検討，早晩日本でも認可が予想される放射線免疫療法の位置づけも重要な検討課題と考えられる．

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血液・腫瘍科，55(3)：294-297，2007

特集 プロテアソーム阻害剤ボルテゾミブの臨床導入

多発性骨髄腫に対するボルテゾミブの国外臨床試験の実施状況*

大間知 謙**

Key Words：myeloma, bortezomib, clinical trial

はじめに

Bortezomibは，米国で行われた第I相試験において治療抵抗性の多発性骨髄腫患者に高い抗腫瘍効果が認められたことから，多発性骨髄腫に対する治療開発が進んできた．再発・難治例を対象とした第II相試験で30%強という高い奏効割合が認められ，dexamethasone単独投与を対象としたランダム化第III相比較試験においては，完全寛解率を含めた奏効割合のみならず，無増悪生存期間および1年全生存率でもdexamethasone単独投与群を上回ったことが報告され，多発性骨髄腫の救援療法における標準的な薬剤の1つとなった．

現在の多発性骨髄腫に対する治療は，寛解導入療法，(適応のある場合は)自家造血幹細胞移植併用の大量化学療法，維持療法，再発・難治例に対する救援療法の4群に大別して考えることができる．多発性骨髄腫治療の中心的な薬剤の1つになりつつあるbortezomibが，それぞれの状況でどのように応用されていくかを現在海外で行われている臨床試験から考察してみる．

National Cancer Instituteのホームページ内のclinical trials database(http://www.cancer.gov/clinicaltrials/search)より，「multiple myeloma / plasma cell neoplasm」「bortezomib」をkey wordにして現在進行中の臨床試験(表1)を検索した．2007年6月現在，49のbortezomibを用いた治療研究が行われている．内訳は，第IV相が1，第III相が11，第II相が24，第I～II相が13となっている．

再発・難治例に対する応用

再発・難治例の多発性骨髄腫に対して3割強の奏効割合が認められたbortezomibであるが，それでも従来の標準的な救援療法の1つである高用量のdexamethasoneに対して，time to progressionの中央値106日に対する189日，1年全生存割合66%に対する80%と，劇的な改善というわけではなかった[1]．さらに生存期間を延長させるために，多発性骨髄腫に対しての有効性が認められている他剤との併用療法が検討されるのは当然の流れであろう．

第I/II相および第II相試験では，新規の分子標的薬との併用療法の検討がいくつか行われている．骨髄腫細胞のリン酸化を阻害することで抗腫瘍効果を発揮するのみでなく，bortezomibの作用を増強する[2]perifostine, superoxide dismutase 1(SOD1)を阻害することで骨髄腫細胞に対してアポトーシスを誘導することが確認されている[3]，抗血管新生の薬剤であるATN-224，ヒストン脱アセチル化酵素阻害剤であり，骨髄腫細胞のBCL-2 familyの発現を減弱させることが知られている[4]depsipeptideや，bortezomibのプロテ

* The aspect of the clinical trial testing bortezomib for multiple myeloma in the world.

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表1 現在進行中のbortezomibを用いた臨床試験

	再発・難治例を対象とした臨床試験	
第 I/II 相	＋liposomal doxorubicin, melphalan	Hervert Irving Comprehensive Cancer Center
	＋ATN-224(SOD1阻害剤)	Pharmaceutical company sponsored
	＋depsipeptide(HDAC阻害剤)	Peter MacCallum Cancer Center /Barbara Ann Karmanos Cancer Institute
	＋arsenic torioxide, ascorbic asid	MD Anderson Cancer Center
	＋SAHA(HDAC阻害剤)	Pharmaceutical company sponsored Greenebaum Cancer Center
	＋Sm 153(radioisotope)	Pharmaceutical company sponsored
第 II 相	効果，骨形成に関する最小量の検討	Arkansas Cancer Research Center
	tandem transplantにおけるconditioning	H. Lee Moffitt Cancer Center
	perifostine(リン酸化阻害剤)，dexametyasone	Pharmaceutical company sponsored
	＋mapatumumab(TRAIL1 agonist)	Pharmaceutical company sponsored
	＋doxorubicin, dexamethasone	Korean Myeloma Working Party /Pharmaceutical company sponsored
	＋dexamethasone	Peter MacCallum Cancer Center /Sparrou Regional Cancer Center
	alternative scheduleの検討	West Clinic-East Menphis
	＋lenalidomide, dexamethasone	Dana-Farber Cancer Center
	＋CNTO 328(抗IL-6キメラ抗体)	Pharmaceutical company sponsored
	PXD101(HDAC阻害剤)	Pharmaceutical company sponsored
	＋bevacizumab(抗VEGF抗体)	Hackensack University Pharmaceutical company sponsored
第 III 相	VTD vs VTD/doxorubicin	Arkansas Cancer Research Center
	VTD vs TD	EBMT solid tumor working party
	未治療例を対象とした臨床試験	
第 II 相	＋ascorbic acid, melphalan	Pharmaceutical company sponsored
	VTD followed by MPT	Korean Myeloma Working Party
	VAD, VTD followed by HDT, bortezomib maintenance	Korean Myeloma Working Party
	＋cyclophosphamide, dexamethasone, thalidomide	Fred Hutchinson Cancer Center
第 III 相	Total Therapy II vs VDTPACE, MEL200, Dexa, Thal, HDT	Arkansas Cancer Research Center
	MP vs MP/bortezomib	Pharmaceutical company sponsored
	bortezomib, dexamethasone vs VAD, followed by HDT	IFM group
	MP/bortezomib vs MP/thalidomide	Program for the study and treatment of Hematological Malignancies；Spain
	VBMCP/VBAD, bortezomib vs thalidomide, dexamethasone vs thalidomide, dexamethasone, bortezomib	Program for the study and treatment of Hematological Malignancies；Spain
	維持療法に関する臨床試験	
第 I 相	HDT後のadjuvant bortezomib	Pharmaceutical company sponsored /Barbara Ann Larmanos Cancer Institute
第 II 相	HDT後のadjuvant bortezomib	Kinderklinik Wuerzburg /Memorial Sloan-Kettering Cancer Center
第 III 相	HDT後のadjuvant bortezomibの有無	Pharmaceutical company sponsored /Copenhagen University Hospital
	高齢者におけるadjuvant bortezomibの有無	Pharmaceutical company sponsored

(http://www.cancer.gov/clinicaltrials/searchより)

アソーム阻害作用の感受性を増強させる[5]suberoylanilide hydroxamic acid(SAHA)，PXD101，骨シンチに用いられる放射性同位元素の1つであり，bortezomibと併用することで相乗効果が指摘されている[6]samarium Sm 153 lecidronam pentasodium, BCL-2 familyを過剰発現している細胞をアポトーシスに誘導する亜ヒ素酸と，その効果を増強するアスコルビン酸[7]，tumor necrosis factor-related apoptosis-inducing ligand receptor-1(TRAIL1)へ結合する，ヒト化アゴニストーモノクローナル抗体であるmapatumumab, vascular endothelial growth factor(VEGF)に対する

モノクローナル抗体であるbevacizumab, IL-6に対するキメラ抗体であるCNTO 328との併用などが検討されている．そのほかにもすでに多発性骨髄腫に対して高い効果が確認されているlenalidomide, 従来から広く骨髄腫治療に用いられているdoxorubicin, dexamethasoneなどとの併用療法の試験が行われている．

第III相試験としては，bortezomib, thalidomideとdexamethasoneの併用療法にdoxorubicin併用の有無を比較したもの(VTD＋/－ doxorubicin)がArkansas大学で，thalidomideとdexamethasoneの併用療法にbortezomib併用の有無を比較した試験(VTD vs. TD)がEBMT solid tumor working partyで進行中であり，多発性骨髄腫に対するkey drugを併用することで，さらに生存期間を延長させられるかどうかが検討されている．また，これらの第I～II相試験で高い効果が確認され，将来的に第III相試験へと発展し，やがては再発・難治例のみならず，初発例に対しても応用されていくことが期待される．

寛解導入療法への応用

多発性骨髄腫に対するこれまでの標準的な寛解導入療法であるMP療法やVAD療法でも50～80％という高い奏効割合が期待できるが，多発性骨髄腫において寛解導入療法の奏効割合は予後と相関しないことも知られている[8]．しかし，これらの治療により完全寛解が得られることはきわめて稀である．寛解導入療法の目的は可能なかぎりの腫瘍量の減少であるが，十分な腫瘍量の減少が得られないため予後につながらない可能性もある．近年，bortezomibを寛解導入療法の一部へ組み込んだ治療法の報告がされるようになり，その高い治療効果が注目されている．Bortezomib単剤またはdexamethasone併用療法，bortezomib, doxorubicin, dexamethasoneの併用療法による寛解導入の報告があるが，前者では完全寛解が6～21％，後者では24％というきわめて高い治療効果が報告されている[9)～11)]．寛解導入療法後には自家末梢血幹細胞採取が行われ，いずれも十分な量の末梢血幹細胞の採取が可能であったとされている．さらに文献11の報告は，大量化学療法を含めたすべての治療が完遂した後の治療効果は，完全寛解が43％(免疫固定法のみ陽性の例が14％)というきわめて良好な結果であった．現時点では長期的な治療効果は不明であるが，これまでの治療では得られないきわめて高い効果であり，そのような深い寛解が長期予後につながる可能性も期待される．その他の，現在進行中の寛解導入療法としての第II相試験としては，アスコルビン酸とmelphalan, thalidomideとdexamethasone, cyclophosphamideとdexamethasoneおよびthalidomideとの併用，VAD療法とbortezomib, thalidomide, dexamethasone併用のsequentialな寛解導入療法などが行われている．寛解導入療法の治療レジメンを比較した第III相試験は，6つの試験が進行中である．Arkansas大学で行われている，多剤併用化学療法であるtotal therapyにbortezomibを組み込んだもの，企業主導で行われているMP療法＋/－bortezomibの比較，フランスのIFMグループで行われているVAD療法とbortezomib＋dexamethasoneの比較，スペインのグループで行われているMP＋bortezomibとthalidomide＋predonisone＋bortezomibの比較，多剤併用化学療法にbortezomibを組み込んだもの，thalidomide＋dexamethasone, thalidomide＋dexamethasone＋bortezomibの3群比較の試験などがある．これらの比較試験は，若年者を対象としたものは原則として自家造血幹細胞移植併用の大量化学療法が行われるプロトコールとなっており，多発性骨髄腫に対する寛解導入療法は，適応があるなら大量化学療法を行うことが依然として標準的治療であると考えられているようである．しかし今後，これらの新規寛解導入療法が長期寛解を得られるという結果が認められるようなら，将来的には大量化学療法の有無について検討する比較試験が計画されるようになるかもしれない．

維持療法への応用

完全寛解を得ることが困難な多発性骨髄腫では，Mタンパクがplateauまで低下した場合，治療を継続してもそれ以上の改善が得られることはない．よって多発性骨髄腫には，いつまで継続するべきかという議論がなされてきた．MP療

法を継続することが無治療で経過観察するよりも寛解期間を長く維持することができるが，無治療経過観察後の増悪に対して再びMP療法を行っても予後に違いはないともされている．よって寛解導入療法後は，watchful waitingもしくは病勢のコントロールを目的とした維持療法が行われることが多い．維持療法の試験としては，大量化学療法後のbortezomib単独またはdexamethasone併用療法の第 I/II 相および第 II 相試験が，大量化学療法後の維持療法としてのbortezomib投与の有無を比較した第 III 相試験が現在行われている．

Bortezomibは，大規模比較試験により再発・難治例の多発性骨髄腫に対する新たな標準的な薬剤であることが示されて以来，救援療法以外にも寛解導入療法や維持療法への応用が進んでいる．ほかにもthalidomideやlenalidomide，それ以外にも骨髄腫に対して有効性が見出されている新規薬剤が複数あり，進歩の乏しかった多発性骨髄腫の治療も，今後大きく変化していくことであろう．不良な血液疾患の代表である多発性骨髄腫の予後が改善していくことを期待したい．

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FOURTH EDITION

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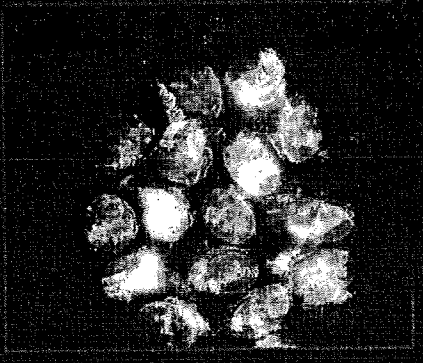

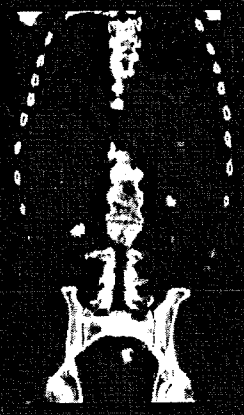

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14 Adult T-Cell Leukemia-Lymphoma

Kensei Tobinai and Toshiki Watanabe

SUMMARY OF KEY POINTS

Background
- Adult T-cell leukemia-lymphoma (ATLL) is a distinct peripheral T-cell malignancy that is associated with human T-cell leukemia virus type I (HTLV-I).

Virology
- HTLV-I is reverse-transcribed into DNA and integrated into the host cell.
- The HTLV-I genome encodes two unique regulatory proteins—Tax and Rex—that are responsible for viral expression and cellular transformation. Tax *trans*-activates viral and cellular genes that could be involved in the pathogenesis of ATLL.

Epidemiology
- The major cluster of HTLV-I-infected individuals and patients with ATLL exists in Japan, where approximately 1.2 million people are infected with the virus.
- Other clusters have been noted in the Caribbean islands (African), tropical Africa (African), South America (Mongoloid), and northern Oceania (Melanesian).
- HTLV-I is transmitted by mother to child through breast-feeding, by sexual contact, and by blood-borne transmission.
- The estimated cumulative risk of the development of ATLL in HTLV-I-positive individuals is 2.5%.

Clinical Manifestations
- Patients with ATLL show diverse clinical features, and four clinical subtypes have been recognized: acute, lymphoma, chronic, and smoldering types.
- The typical manifestations of acute-type ATLL include circulating neoplastic cells in the peripheral blood, generalized lymph node swelling, hepatosplenomegaly, skin involvement, and hypercalcemia.

Histopathology
- Leukemic cells in the peripheral blood characteristically show markedly polylobated nuclei, the so-called flower cells. Their immunophenotypes are CD4-positive and CD8-negative T-cell in most cases.
- All histopathologic specimens show the findings of peripheral T-cell lymphoma of various subtypes.

Diagnosis
- ATLL is suspected when the aforementioned characteristic clinical manifestations and/or the cytologic findings of leukemic cells in the peripheral blood are recognized.
- An immunophenotypic analysis of neoplastic cells and a serologic assay against HTLV-I are required for the clinical diagnosis of ATLL.
- The demonstration of the monoclonal integration of HTLV-I proviral DNA in the tumor cells can lead to a definite diagnosis of ATLL.

Treatment
- An accurate diagnosis of the clinical subtype is vital for appropriate decisions regarding treatment.
- Combination chemotherapies used in the treatment of non-Hodgkin's lymphoma are usually given to patients with the acute or lymphoma subtype of ATLL; however, most patients with ATLL are not curable with current chemotherapy regimens.
- Further efforts to incorporate new, innovative treatment modalities, such as new anticancer agents, monoclonal antibody therapy, molecular-targeting therapy, and allogeneic hematopoietic stem cell transplantation, are needed.

INTRODUCTION

Adult T-cell leukemia-lymphoma (ATLL) was first recognized in Japan in 1977s.[1] The disease was characterized as leukemia of peripheral T cells, generalized lymphadenopathy, hepatosplenomegaly, and skin involvement. Owing to its unusual geographic clustering in southwestern Japan, it was postulated that some infectious agent(s) had causative roles. Human T-lymphotropic virus (HTLV) was first isolated by Poiesz and associates[2] in the United States from cultured cells from one patient with an aggressive variant of mycosis fungoides and from one with Sézary syndrome. Although both patients were diagnosed clinically as having cutaneous T-cell lymphoma (CTCL) at the time of reporting, their clinical features were later found to closely resemble those of Japanese patients with ATLL.

In 1980, Miyoshi and coworkers[3] established the first cell line (MT-1) derived from neoplastic cells in an ATLL patient. They cocultured neoplastic cells from an ATLL patient with normal human cord blood lymphocytes and established the cell line MT-2 (derived from cord blood lymphocytes), which produced high amounts of type C retrovirus.[4] Using the MT-1 cell line, Hinuma and colleagues[5] found that patients with ATLL had antibodies against the virus-associated antigen in their sera. The "ATLL virus" was then isolated and characterized as an RNA retrovirus.[6] As HTLV and ATLL virus were found to be identical by a DNA sequence analysis, this virus was designated human T-cell leukemia virus type I or human T-lymphotropic virus type I (HTLV-I).[7]

The etiologic association of HTLV-I and ATLL is based on the findings that follow.

- The areas of high incidence of patients with ATLL closely correspond with those of high prevalence of HTLV-I carriers.[8]
- HTLV-I immortalizes T cells in vitro.[9]
- HTLV-I proviral DNA is detected in the neoplastic cells of ATLL.[10]
- Almost all patients with ATLL have antibodies against HTLV-I in their sera.

HTLV-I is the first retrovirus that was found to be associated with a malignant neoplasm in humans.

VIROLOGY AND PATHOGENESIS

HTLV-I is reverse-transcribed into DNA and integrated as a proviral DNA in the host cell. The HTLV-I provirus is 9.0 kilobases long and has structural genes in the order 5′-gag-pol-env-3′. Both ends of the HTLV-I proviral DNA contain repeats called long terminal repeats (LTRs). No specific integration sites of the HTLV-I provirus in the host cellular chromosomes have been identified.[11] A unique feature of the viral structure of HTLV-I provirus is the presence of a long sequence between *env* and 3′ LTR. One product of this *pX* gene, p40*tax*, acts on the LTRs for the *trans*-activation of the viral gene.[12]

The HTLV-I gene encodes three structural proteins: group antigen (*gag*), reverse transcriptase (*pol*), and envelope (*env*) proteins. The full-length mRNA is used for synthesis of *gag* and *pol* gene products. The gag protein is synthesized as a precursor polypeptide of 55 kilodaltons that is proteolytically cleaved into the individual gag proteins p19, p24, and p15. The protease is encoded in a different reading frame that spans the 3′ part of the *gag* region and the 5′ part of the *pol* region. The *pol* region encodes the reverse transcriptase, integrase, and RNase H. The *env* gene encodes two proteins made from a singly spliced mRNA. It is then cleaved intracellularly into an extracellular glycosylated protein (gp46) and a transmembrane (gp21). The *pX* region at the 3′ end of the genome has the potential to encode essential regulatory proteins (Tax and Rex) and three accessory proteins—p12, p13, and p30—that are important for viral infectivity and replication by influencing cellular signaling and gene expression.[13,14]

The life cycle of a retrovirus begins with the binding of the virus to specific receptors on the cell surface via viral envelope proteins. HTLV-1 is transmitted through a viral synapse and enters target cells via interaction with the glucose transporter GLUT1.[15] However, other molecules have also been reported to be involved in virus entry, for example, HSC70,[16] heparan sulfate proteoglycans,[17] and neurophilin-1.[18]

Role of Tax

The onset of ATLL is preceded by a long period of clinical latency, frequently lasting more than four decades. In addition, fewer than 5% of all infected individuals with HTLV-I develop ATLL. The promoter insertion model was rejected as the leukemogenic mechanism because integration sites of the provirus were random depending on the patient.[11] Consequently, a *trans*-acting viral factor, Tax, has been shown to be oncogenic, since it transforms and immortalizes rodent fibroblasts and T lymphocytes as well as human T lymphocytes. Tax *trans*-activates viral transcription through interaction with the cellular basic domain/leucine zipper transcription factors CREB and ATF-1. Tax interacts with numerous cellular proteins to reprogram cellular processes, including, but not limited to, transcription, cell cycle regulation, DNA repair, and apoptosis. Tax transcriptionally regulates cellular genes by interaction with enhancer-binding proteins such as CREB, NF-κB, and serum response factor and by tethering coactivators to the DNA-bound transcription factors. Tax also stimulates cell growth by direct binding to cyclin-dependent kinase holoenzymes and/or inactivating tumor suppressors such as p53 and DLG. Furthermore, Tax silences cellular checkpoints, which guard against DNA structural damage and chromosomal missegregation, thereby favoring the manifestation of a mutator phenotype in cells.[13,19]

Tax interacts and activates specific components of growth factor signal transduction pathways, such as IKK-IκB-NF-κB, RAS/mitogen-activated protein kinase, protein kinase A, and protein kinase C.[20,21] Interaction with IKKγ, a component of IKK complex, results in constitutive activation of this kinase complex.[22] Constitutive activation of the JAK-STAT pathway in HTLV-I-transformed cells has also been reported, although the mechanisms are not well understood.[23] Thus, HTLV-I infection results in aberrant activation of growth-promoting signaling pathways.

The oncogenic capacity of Tax has been reported in various systems; however, cellular transformation by HTLV-I in vivo is a multistage process, and viral gene expression is absent in ATLL cells in vivo.[24,25] Moreover, proviruses integrated in ATLL cells are frequently defective, have mutations in the coding region of Tax, and/or are methylated in the 5′ and 5′ LTR regions.[26–28] Thus, in addition to promoting growth directly, Tax should endow the infected T cells with capacities that aid the progression to transformed phenotypes in the absence of Tax. In this context, induction of a mutator phenotype by Tax in the infected cells appears to play an important role.[29] The roles of HTLV-I Tax in the multistep leukemogenesis of ATLL are illustrated in Figure 114-1.

Expression of antisense strand RNA with capacity encoding a zinc finger protein (HTLV-I basic leucine zipper factor) has opened a new research field. HTLV-I basic leucine zipper factor inhibits Tax-dependent viral transcription[30] and might be involved in growth of ATLL cells.[31]

Role of Chromosomal Abnormalities

Various karyotypic abnormalities have been reported in neoplastic cells of ATLL; however, no specific karyotypic abnormality has been

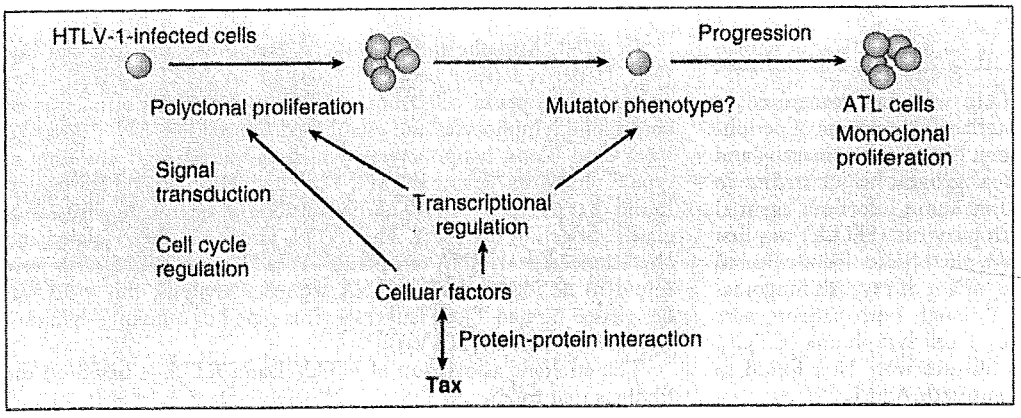

Figure 114-1 • Roles of HTLV-I Tax in the multistep leukemogenesis of ATLL. Tax exerts its biologic effects mainly through protein-protein interaction, resulting in deregulation of transcription, cell cycle control, and signal transduction. It also impairs the cell's ability to repair DNA damage, which can lead to the mutator phenotype of the infected cells.

nd. In general, the chromosomal abnormalities are more complex the acute type compared with those in the chronic type. Itoyama d colleagues[32] reported the results of cytogenetic analysis of 50 cases ATLL and found aneuploidy and multiple breaks more frequently acute and lymphoma types. Multiple breaks and partial loss of omosomes correlated with shorter survival. The authors claim that e model of an oncogenic mechanism—activation of a proto-cogene by translocation of a T-cell receptor (TCR) gene—might be applicable to the main pathway of development of ATLL and at a multistep process of leukemogenesis is required.

In a study by Tsukasaki and associates,[33] 64 patients with ATLL re analyzed by using comparative genomic hybridization (CGH). e most frequent observations were gains at chromosomes 14q, 7q, d 3p and losses at chromosomes 6q and 13q. Chromosome imbal-ces, losses, and gains were observed more frequently in acute or mphoma types. An increased number of chromosomal imbalances re associated with a shorter survival. Paired samples (i.e., samples ained at different sites from four patients) and sequential samples m 13 patients (from six during both chronic phase and acute crisis d from seven during both acute onset and relapse) were examined CGH and Southern blotting for HTLV-I. All but two paired mples showed differences on CGH assessment. Two chronic/crisis mples showed distinct results regarding both CGH and HTLV-I tegration sites, suggesting clonal changes in ATLL at crisis. In 11 tients, the finding of identical HTLV-I sites and clonally related GH results suggested a common origin of sequential samples. In ntrast to chronic/crisis samples, CGH results with all acute/relapse mple pairs showed the presence of clonally related but not evolu-nal subclones at relapse. It was concluded that clonal diversity is mmon during progression of ATLL and that CGH alterations are ociated with clinical course.

ole of *p53* and Other Tumor Suppressor Genes

3 is a nuclear phosphoprotein that functions as a tumor suppressor ne. A loss of normally functioning *p53* through mutation or allelic s has been found in several kinds of malignant neoplasms. Muta-ns of the *p53* gene have also been found in some patients with TLL.[34,35] According to the study by Cesarman and coworkers,[35] no 53 mutations were detected in samples from 11 patients with the ronic type of ATLL, whereas 9 (28%) of 28 samples from patients th the acute type of ATLL exhibited p53 mutations. In one patient, tumor sample obtained during the chronic phase did not have a tation of the p53 gene, but the mutation was subsequently tected in a sample that was obtained at crisis. These results suggest t alterations of the p53 gene might contribute to disease progres-n in a fraction of patients with ATLL.

Other putative tumor suppressor genes, $p15^{INK4B}$ and $p16^{INK4A}$, re reported to be associated with ATLL.[36–38] Yamada and associ-s[37] reported that 28 (25%) of 114 patients with ATLL showed mozygous deletions of the *p15* and/or *p16* genes. These results related well with the clinical subtypes of ATLL. In addition, the tients with deleted *p15* and/or *p16* genes showed significantly rter survival than did patients in whom both genes were preserved < 0.0001). Moreover, three of the five chronic-type patients who gressed to acute-type ATLL lost the *p16* gene alone or both genes their exacerbation phase. These results suggest that the deletions *p15* and/or *p16* genes play a key role in the disease progression of ne patients with ATLL. Uchida and colleagues[38] found the point tation of the *p16* gene in 3 (7%) of 44 patients with ATLL. It is ggested that the *p16* gene is inactivated not only by homozygous tion, but also by point mutation.

ole of HTLV-I Provirus

veral investigators have analyzed the implications of the integration ttern of HTLV-I provirus in the disease progression of ATLL.[39,40] s known that the neoplastic cells of ATLL have one copy of complete HTLV-I provirus per cell in some patients (complete-type), while others have multiple complete copies of the virus per cell (multiple-type). The HTLV-I proviruses in the remaining patients do not have the complete genome but rather have a defective genome (defective-type). Tsukasaki and associates[40] found that the median survival times (MST) for patients were 7 months, 24 months, and 33 months for defective-type, complete-type, and multiple-type ATLL, respectively ($P = 0.006$). Among 52 sequentially examined patients, the HTLV-I integration patterns changed in four patients (8%). In three of these four, the rearrangements of the TCR-β gene changed concomitantly, suggesting the appearance of a new ATLL clone. The researchers concluded that the frequent clonal change of ATLL at crisis reflects the emergence of multiple premalignant clones in viral leukemogenesis.

Tamiya and coworkers[39] reported the presence of two types of defective virus. Among them, type 2 defective virus with the deletion that includes 5′ LTR was found more frequently in the acute and lymphoma types (39%, 21 of 54) than in the chronic type (6%, 1 of 18). It is postulated that the high frequency of the type 2 defective viruses is caused by the genetic instability of HTLV-I provirus and that this defective virus is selected because it escapes from the immune surveillance system in the host.

HTLV-I is an etiologic agent not only in ATLL, but also in the neurologic disorder known as tropical spastic paraparesis (TSP) or as HTLV-I-associated myelopathy (HAM).[41,42] In TSP/HAM, the HTLV-I provirus remains randomly integrated, whereas in ATLL, the provirus is monoclonally integrated.

EPIDEMIOLOGY OF HTLV-I AND ADULT T-CELL LEUKEMIA-LYMPHOMA

Southwestern Japan has the highest recorded prevalence of HTLV-I infection and the highest incidence of patients with ATLL in the world.[8,42–44] A high prevalence of HTLV-I is also found in the Caribbean islands (African), tropical Africa (African), South America (Mongoloid), and northern Oceania (Melanesian).[43–46] Many patients who have been diagnosed as having ATLL in Western countries are immigrants from the West Indies and tropical Africa. The world map of the distribution of HTLV-I and HTLV-II and the presumed routes of spread are shown in Figure 114-2.[44] The geographic clustering of HTLV-I carriers is suggested to be strongly associated with a high frequency of mother-to-child transmission of the virus under closed conditions in particular groups.[47]

It has been estimated that approximately 1.2 million HTLV-I-infected individuals reside in Japan, and the annual incidence of ATLL has been estimated to be approximately 700 in Japan.[8] The annual rate of ATLL development among HTLV-I 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 ATLL development among the HTLV-I carriers is estimated to be 2.5% to 5% over the course of a 70-year life span.[48]

In a national survey in Japan, the mean age of patients with ATLL has been estimated at 57.6 years, and this age appears to have increased over time.[8] It has been reported that the age of patients with ATLL in areas outside Japan is somewhat lower, with an overall mean age in the mid-forties.[49] In endemic areas, there is a marked increase in HTLV-I prevalence with age until age 70 years and an increased prevalence among females compared with males. Transmission occurs via sexual and blood-borne routes. A major reason for the increase in seroprevalence with age appears to be the decreasing prevalence of HTLV-I in the population over time, at least in Japan, where it has been most extensively studied. Yamaguchi and coworkers[50] reported that the HTLV-I carrier rates among blood donors in Japan had fallen since 1986 in all age groups under 50 years and in both genders. This decrease in HTLV-I carriers among younger blood donors might be explained by improvements in sanitation and general lifestyle changes in recent years. A shorter duration of breast-feeding,

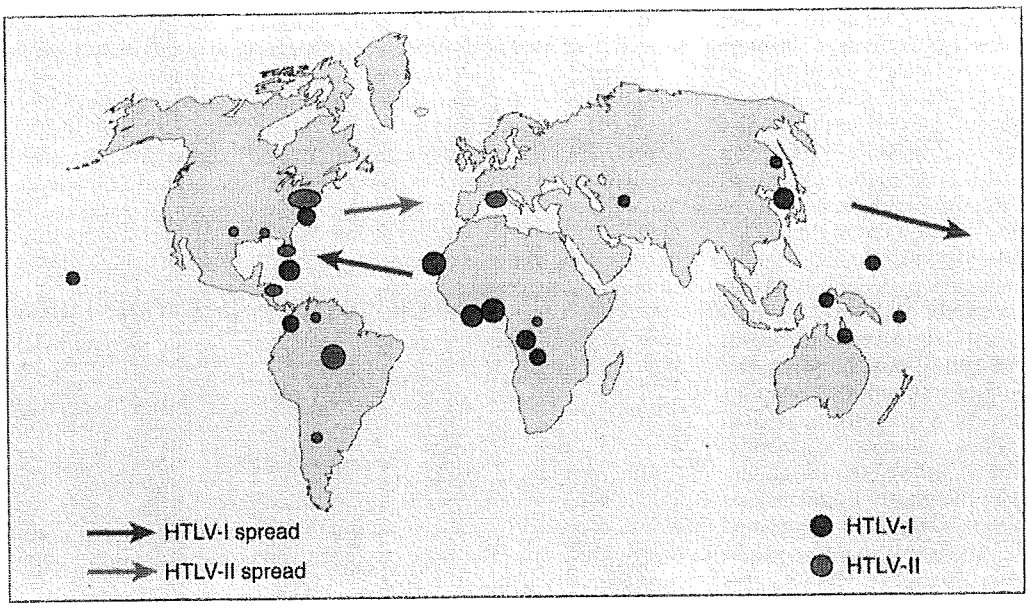

Figure 114-2 • World map of HTLV distribution and its presumed routes of spread. (From Blattner WA, Gallo RC: Epidemiology of HTLV-I and HTLV-II infection. In Takatsuki K [ed]: Adult T-cell Leukaemia. Oxford, UK, Oxford University Press, 1994, p 45. Prepared by Dr. Robert J Biggar, National Cancer Institute, USA.)

the increasing use of artificial feeding for babies, and decreasing family size are also likely to be factors for the recent decline in the vertical transmission rates of HTLV-I.[50] Overall, there is a slight male predominance of ATLL patients, the male-to-female ratio ranging from 1.1 to 1.5. This is in contrast to TSP and HAM, which affect females more frequently than males.

It has been shown that HTLV-I is transmitted by at least three routes:

1. Mother-to child-transmission, mainly by HTLV-I-positive lymphocytes in breast milk.[51]
2. Sexual transmission, more commonly from males to females.
3. Blood-borne transmission, including blood transfusions and sharing of needles by intravenous drug abusers.[52,53]

The first route is vertical transmission from mother to child via HTLV-I-positive lymphocytes in breast milk. The overall infection rate of HTLV-I in children by seropositive mothers has been estimated to be 10% to 30%. HTLV-I infection has also been reported in children who had not been breast-fed, however, which suggests the possibility of intrauterine or transvaginal infection. Several kinds of intervention trials are being conducted in HTLV-I-endemic areas in Japan, where seropositive pregnant women are advised not to breast-feed.[47]

The second route is transmission through sexual contact. Transmission of HTLV-I frequently occurs from male to female but rarely from female to male. HTLV-I has been isolated in semen. It appears likely that the risk of development of ATLL after HTLV-I infection by this route of transmission is not high.

To prevent HTLV-I transmission through blood transfusions, serologic screening of all blood donors for HTLV-I has been conducted in Japan since November 1986. Inaba and coworkers[54] reviewed the effectiveness of the donor screening in preventing transmission of HTLV-I through blood transfusion in Japan. Seroconversion was found in only 1 of 4672 transfused patients, but the donor was confirmed to be negative for anti-HTLV-I antibody and virus genome by nested polymerase chain reaction (PCR). A total of 23,323 red cell concentrates and 17,237 platelet concentrates were transfused to these 4672 patients. Therefore, the anti-HTLV-I prevalence in blood for transfusion after screening was estimated at 1 in 45,560 (0.0022%; the upper 95% confidence interval (CI) was 0.0080%). This study confirmed that the present donor screening program for HTLV-I can almost completely prevent virus transmission by transfusion in Japan. In contrast to red cell and platelet concentrates, fresh-frozen plasma and plasma fractions have never been shown to transmit HTLV-I.

From the viewpoint of the epidemiologic aspects of HTLV-I and ATLL, several points can be made in ATLL leukemogenesis:

- Viral infection alone is not adequate for the expression of the malignant phenotype.
- The timing and/or length of viral exposure is critical.
- The long latency period suggests that the disease progression is a multistep process. This is in contrast to TSP/HAM, which can occur with a shorter latency period, especially among recipients of blood transfusions.

CLINICAL MANIFESTATIONS

After HTLV-I was revealed to be associated with ATLL, it was found that ATLL shows a marked diversity in its clinical manifestations. ATLL cases have been subdivided into four distinct clinicopathologic entities: acute, lymphoma, chronic, and smoldering types. The recognition of the four clinical subtypes is important in understanding the natural history, clinical features, treatment strategy, and leukemogenesis of ATLL. On the basis of the nationwide survey of 854 patients with ATLL who were diagnosed between 1983 and 1987 in Japan, the Lymphoma Study Group proposed the diagnostic criteria of the four clinical subtypes (Table 114-1):[55]

1. The acute type shows a rapidly progressive clinical course and most of the characteristic features of ATLL: generalized lymphadenopathy, hepatomegaly, splenomegaly, skin involvement, hypercalcemia, and organ infiltration (lung, gastrointestinal tract, etc.). The symptoms and signs include abdominal pain, diarrhea, ascites, pleural effusion, cough, sputum, and chest x-ray abnormalities.
2. The smoldering type shows an indolent clinical course and only a small percentage of leukemic cells, but it also can include skin involvement.
3. The chronic type, with a high percentage of leukemic cells, is occasionally associated with skin involvement, lymphadenopathy, and hepatosplenomegaly and also shows an indolent clinical course.
4. The lymphoma type includes patients who present with the manifestations of non-Hodgkin's lymphoma (NHL) without circulat-

Table 114-1 Diagnostic Criteria for Clinical Subtypes of Adult T-Cell Leukemia-Lymphoma

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

HTLV-I, human T-lymphotropic virus type I; LDH, lactate dehydrogenase; N normal upper limit.
*No essential qualification except terms required for other subtype(s).
†Typical "flower cells" may be seen occasionally.
‡Accompanied by T lymphocytosis ($3.5 \times 10^3/\mu L$ or more).
§If abnormal T lymphocytes are less than 5% in peripheral blood, histologically proven tumor lesion is required.
¶Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood.
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.

ing malignant cells in the peripheral blood. When patients with ATLL are staged according to the Ann Arbor classification, most patients are categorized as stage IV, because leukemic cells are recognized even in clinically indolent forms such as the smoldering type and chronic type. Therefore, in ATLL, the clinical subtype is more important than the Ann Arbor stage for predicting prognosis and determining appropriate treatment strategies for individual patients.

ATLL, particularly the aggressive forms (acute and lymphoma types), has been found to infiltrate the stomach and the intestines in 29% and 25% of patients, respectively, at autopsy.[56] The involvement may be focal as an isolated gastric lesion or so diffuse as to involve the entire gastrointestinal tract. Extensive infiltration of the intestines can lead to moderate to severe diarrhea and malabsorption. Patients with ATLL suffer from a variety of abdominal symptoms (e.g., nausea, vomiting, abdominal fullness, and diarrhea), which might be attributable to infiltration by neoplastic cells, but because of the associated immunodeficiency, various opportunistic infections such as Strongyloidiasis can complicate cases.

Hepatic involvement of ATLL cells can be found in up to one fourth of patients with acute and lymphoma subtypes and not infrequently manifests with jaundice and hepatic transaminase elevations. Yamada and coworkers[57] examined 111 patients with acute-type or lymphoma-type ATLL and compared them with 106 patients with NHL other than ATLL. Among patients with ATLL, there were more frequent palpable hepatomegaly, higher total bilirubin, hepatic transaminase, LDH, and alkaline phosphatase values than among other NHL patients. Autopsy liver samples disclosed that the portal area was most frequently infiltrated with ATLL cells.

Pulmonary complications, which are common in ATLL, are due to leukemic infiltration in one half of patients and to infections with a variety of bacterial and opportunistic organisms in the other half.[58] Of 854 Japanese patients with ATLL, 26% had active infections at the time of diagnosis.[55] The incidence was highest among patients with the chronic and smoldering types (36%) and lower for patients with the acute (27%) and lymphoma (11%) subtypes. The infections that were encountered were bacterial (pneumonias, sepsis, and tuberculosis) in 43%, fungal in 31%, protozoal in 18%, and viral in 8% of patients with ATLL (Table 114-2). The immunodeficiency at presentation in ATLL can be exacerbated by the neutropenia that is produced by cytotoxic chemotherapy, leading to an extremely high risk of infection throughout the course of therapy. Infections are responsible for the patient's death in about half of the cases.

Central nervous system involvement occurs in approximately 10% of patients with ATLL. Teshima and associates[59] identified 15 instances of central nervous system involvement in 10 of 99 patients with ATLL. Leptomeningeal involvement was present in 9 of 10 patients, intracerebral infiltration was noted in 3, and the spinal cord was involved in 2. The initial symptoms included muscle weakness (47%), altered mental status (47%), paresthesias (40%), headache (33%), and urinary incontinence (27%). Signs included nuchal rigidity (33%) and cranial nerve palsies (13%). Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone was observed in four patients.

Table 114-2 Infectious Complications at Diagnosis in 818 Japanese Patients with Adult T-Cell Leukemia-Lymphoma

Infection	No. of Patients*				
	Acute	Lymphoma	Chronic	Smoldering	Total
Bacterial infection	(55)	(9 + 1)†	(25)	(4)	(93)
Pneumonia	35‡	1	14	4	54
Pyoderma	1	1	3	0	5
Septicemia	6	0	1	0	7
Tuberculosis	7	1	3	0	11
Other	6	6	4	0	16
Fungal infection§	(36 + 2)‡	(6)	(16)	(8)	(66)
Cutaneous	26	5‡	12	5	48
Oral	2	0	0	0	2
Esophageal	2	0	2	1	5
Pulmonary	5	1	1	0	7
Meningitis	1	0	1	2	4
Protozoal infection¶	(22)	(2)	(10)	(4)	(38)
Strongyloidiasis	13‡	2	5	1	21
Giardiasis	1	0	0	0	1
Pneumocystis carinii	8	0	5	3	16
Viral infection#	(13)	(0)	(3)	(0)	(16)
Herpes zoster	7	0	2	0	9
CMV pneumonia	3	0	0	0	3
Pneumonitis	2	0	1	0	3
Condyloma acuminatum	1	0	0	0	1
No infection**	339	139	98	29	605
Total	465	156	152	45	818

CMV, cytomegalovirus.
*Numbers in parentheses indicate total number of patients in each category.
†One patient had leprosy.
‡One patient each suffered from oral candidiasis.
§$P < 0.05$.
¶$P < 0.01$.
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;79:42.

LABORATORY FINDINGS

Laboratory findings also depend on the clinical subtype of ATLL (see Table 114-1).[55] Leukocytosis is found among patients with the acute or chronic subtype at presentation, exhibiting characteristic atypical lymphoid cells with markedly lobated nuclei, termed *flower cells*. Although not all patients present with a leukemic feature, peripheral blood involvement develops in most patients at some time during the course of their disease. Most patients with the acute or lymphoma subtype of ATLL have elevated serum LDH levels.

The most striking laboratory finding in patients with ATLL is hypercalcemia, which was evident in 32% of Japanese patients with ATLL.[55] Multiple factors have been suggested to contribute to the development of hypercalcemia. Lytic bone lesions have been described in some patients; however, examinations of bone obtained at autopsy or from bone marrow biopsies usually reveal activated osteoclasts with increased bone resorption; infiltrating neoplastic T cells are rarely found. Patients with ATLL have low phosphate levels, hypercalciuria, high levels of nephrogenous cyclic adenosine monophosphate, and low levels of 1,25-dihydroxyvitamin D. This pattern suggests the presence of humoral hypercalcemia of malignancy, which was found to be secondary to the production of a parathyroid hormone (PTH)-like molecule by malignant cells. HTLV-I-infected cells were found to produce a protein with PTH-like activity, such as PTH-related peptide.[60–62] Another suggested contributor to hypercalcemia in patients with ATLL is cytokine production by the tumor cells. HTLV-I-infected cell lines and fresh ATLL cells from hypercalcemic patients produce TNF-α, TNF-β, IL-1α, and IL-1β. Each of these cytokines can enhance osteoclast activity and bone-resorbing activity in animal models. Ishibashi and colleagues[63] demonstrated elevated serum levels of TNF-β in seven of eight patients with ATLL who had complications of hypercalcemia and in none of 28 patients with ATLL who had normal serum calcium levels.

Nosaka and coworkers[64] analyzed the expression of various genes that were suggested to regulate serum calcium levels in ATLL and reported that the overexpression of the receptor activator of NF-κB (RANK) ligand gene correlated with hypercalcemia. ATLL cells from patients with hypercalcemia, which highly expressed the transcripts of the RANK ligand (RANKL) gene, induced the differentiation of human hematopoietic precursor cells (HPCs) into osteoclasts in vitro in the presence of macrophage colony-stimulating factor. In contrast, ATLL cells from patients without hypercalcemia did not induce such