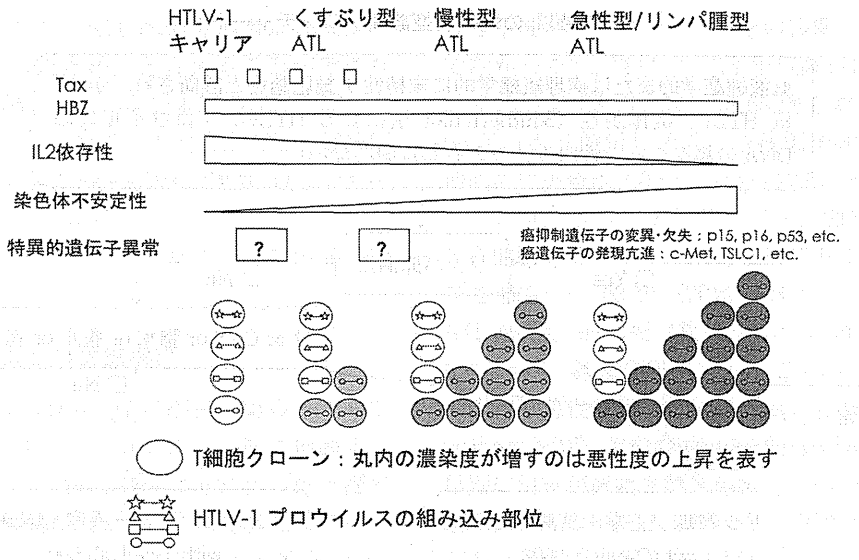

図2 成人T細胞白血病リンパ腫の多段階発癌のメカニズム

の場合は，同じ方法でより複雑な染色体異常が検出された。一方，急性型ATLの場合はコロニーを形成しなかったことから，キャリア，Indolent ATLと異なりIL2依存性にはコロニー増殖をしないことが明らかとなった。そこで間質細胞との接着の意義について，マウスのストローマ細胞株（MS5）と急性型ATLの末梢血単核球を共培養して検討したところ，接着する場合に限って，興味深いことに生体内と同様にHTLV-1を発現することなくATLクローンのコロニー形成を認めた[42]。一方，免疫不全マウスのNOD/SCID/γc^{null}では，急性型のみならず慢性型ATLの末梢血単核球が白血病・組織浸潤を引き起こすことから，新規治療法の開発研究で有用である[43]。

無症候性キャリアでも，花弁様の核分葉や濃染する核網構造を持つATLに特徴的な白血病細胞を，特にウイルス量の多いHTLV-1キャリアの末梢血塗抹標本で認めることが知られており，染色体不安定性と核クロマチン構造の変化の関連が示唆される。ATL細胞にaneuploidyや花弁様核形態をもたらす機序としては，mitotic spindle assembly checkpoint機能を持つMAD1とTaxの結合，T細胞活性化に重要なPI3K経路を抑制するPTENとSHIP-1の発現低下による微小管の異常などが報告されている[44,45]。

HTLV-1キャリアにおける個々の遺伝子異常は知られていない。HTLV-1キャリアからのATL発症においては，前述したようにTax蛋白が一過性に発現しtransactivationによりインターロイキン2やその受容体などの発現を誘導し，HTLV-1感染細胞がautocrine的に増殖することが重要であることが示唆されている[14,15]。一方ATL細胞における遺伝子異常としては，細胞周期を制御する蛋白質をコードしている癌抑制遺伝子p53，$p15^{INK4B}$，$p16^{INK4A}$などが急性型/リンパ腫型ATLで高頻度に不活化しており，しばしばこれらの異常は慢性型/くすぶり型ATLの急性転化時に出現する[28,29]。染色体分染法やcomparative genomic hybridization（CGH）法によるATLの数的および構造的染色体異常はランダム，かつ複雑であることが多く，また慢性型/くすぶり型ATLよりも急性型/リンパ腫型ATLで高頻度かつ複雑である[46~48]。急性型とリンパ腫型では，CGHによるゲノム異常パターンが異なることも報告されている[49]。これまでにATLに重要な癌遺伝子としては，アレイ法による網羅的解析でTSLC1，c-METなどの発現亢進が報告されているが，染色体検査で高頻度に増幅が認められる14q32や7q21-q35にも存在する可能性がある[50,51]。ATL細胞でのエピジェネティク変化としては，$p16^{INK4A}$が前述した欠失の他DNAメチル化により転写抑制されている[62]。以上よりATLの多段階発癌においてはHBZの定常的発現の他，前期ではTax蛋白の一過性発現や染色体不安定性が，後期ではいくつかの癌抑制遺伝子の変異・欠失とエピジェネティク変化や癌遺伝子の増幅・発現亢進が，それぞれ重要な因子の一つであると考えられる。ATLの多段階発癌の典型と考えられる模式図を図2に示したが，異なる経過としては，indolentな時期を経ずにaggressive ATLを発症する場合，indolent ATLからHTLV-1キャリアの状態へ戻る場合，indolent ATLとは異なるクローンの出現によりaggressive ATLを発症する場合などが報告されている。

ATLの治療

HTLV-1という病因ウイルスが同定されているATLに

介入する場合，大きく3つのステップ，すなわちHTLV-1感染予防，HTLV-1キャリアにおけるATL発症予防，そしてATLの治療に分けて考えることができる[14,15]。HTLV-1の疫学の項で述べたように，感染予防法はほぼ確立している。発症予防については，前述したように対象としてはキャリアの内ATL発症高リスク群を同定できたが，現時点では発症を予防できうる，例えばHTLV-1ウイルス量を低下させる有効な方法は確立していない。一方，日本に約120万人いるHTLV-1キャリアの中から年間約1,000人が新規に発症すると推定されているATLの標準的な治療法は，残念ながら未だ確立していない。高齢者に多く，また多臓器への浸潤傾向，薬剤耐性，免疫不全が強いことなどが，他の造血器腫瘍と比べて予後不良な要因とされている。

造血器腫瘍の中でも難治性疾患であるATLの治療法は，その臨床病態が多様であることから，低悪性度｛くすぶり型，予後不良因子（LDH，BUNまたはアルブミンが異常値）を持つ慢性型｝と高悪性度（急性型，リンパ腫型，予後不良因子を持たない慢性型）ATLに大きくグループ分けして方針を決定する。日本では低悪性度ATLにはWatchful waiting（WW）が，高悪性度ATLには強力な併用化学療法または同種造血幹細胞移植療法（allo-HSCT）が用いられることが多かった。一方欧米では，ATLがHTLV-1によることから，いずれの病型にもインターフェロンα（IFN）とジドブジン（AZT）の併用療法が汎用されてきた。表3には，2009年にまとめられたATLに対する治療戦略についての国際的合意を示す[53]。以下に，各治療法を概説する。

化学療法

ATLに対しての臨床試験による標準的な併用化学療法の開発には，JCOG-LSGが重要な役割を担ってきた（表4）。初めてのJCOG試験であるATLを含むnon-Hodgkin's lymphoma（NHL）を対象とした1978年からの第2相試験（JCOG7810）では，VEPA（vincristine, cyclophosphamide, prednisolone, doxorubicin; LSG1）療法によるATLの完全寛解（CR）率は17%（3/13）と極めて低かった[54]。1981年より開始したLSG1と更にmethotrexate（MTX）を加えたLSG2（VEPAM）との第3相比較試験（JCOG8101）では，ATLは54例が登録され，そのCR率は28%｛LSG1 17%（4/24），LSG2 37%（11/30）｝と，B-NHLの74%（61/82），ATL以外のT-NHLの73%（16/22）と比べて著しく低かった。さらにはATL患者54例全例での4年生存率も8.3%であった[55]（表4）。1987年からの同じくATLを含む進行期aggressive NHLに対する第2相試験（JCOG8701）で用いられたLSG4は，いわゆるNHLに対する第二世代の治療法であり，LSG1の4剤にMTX，etoposide（ETP），vindesine（VDS），procarbazine，bleomycinの5剤を追加した。このLSG4ではATL患者43例のCR率は42%（18/43）と改善したが，B-NHLの82%（123/151）やATL以外のT-NHLの67%（28/42）と比べてやはり著しく不良であった[56]。さらにはATLの生存期間中央値（MST）は8ヶ月，4年生存率は12%でありJCOG8101までの成績と同様に不良であった（表4）。

1991年にはJCOG-LSGから前述した病型診断規準が提唱され，これが治療法の選択の重要な指標とされるようになった[8]。慢性型に限った解析では，LDH，BUN，アルブミン値が予後不良因子であり，そのいずれかが異常であるとMSTは約15ヶ月であった[57]。1991年から急性型，リンパ腫型または予後不良因子を有する慢性型からなる高悪性度ATLのみを対象として開始された第2相試験JCOG9109での適格規準は，以降のJCOG臨床試験でも用いられた[58]：1）ATLの診断規準としては抗HTLV-1抗体陽性の末梢性T細胞リンパ腫であること；2）前治療がなく15歳から69歳で主要臓器予備能を有し，中枢神経浸潤を認めず，PS3以下（高Ca血症によるPS4は適格）かつHBs Ag/HCV Abが陰性であること。本試験で用いられたLSG11レジメンは，VCR，DOX，ETP，PSLと当時ATLの救済療法で有望な成績を示したdeoxycoformycinの5剤を併用した。適格60例でのCR率28%（17/60），部分寛解（PR）率23%（14/60）であった。grade 4の血液毒性を67%に認め，4例で致死的な感染症を併発した。MSTは7.4ヶ月，2年生存率は17%であり，DCFを組み込みaggressive ATLのみを対象とした本試験結果はそれまでの治療成績と同様に不良であった（表4）[6]。

前述したように，LSG1，LSG2，LSG4レジメンの順に用いる抗癌剤の種類が増すとCR率は高まっていたので，1994年より開始された第2相試験（JCOG9303）のLSG15では，治療の基本となるLSG1にVDS，ETP，さらにはATL細胞で高発現している薬剤耐性遺伝子mdr 1のP糖蛋白が耐性に関与しないranimustineとcarboplatinを組み込み，G-CSFを併用し治療間隔の短縮による治療の増強を図った[59]。さらにはATLの再発部位として中枢神経が高頻度であったので，MTXとPSLを予防的に髄腔内注入した。適格93例でのCR率35%，PR率45%，2年全生存率は31%，MSTは13ヶ月であった（表1）。Grade 4の血液毒性を65%の患者に認めたが，grade 4の非血液毒性は1例のみであった。

JCOG9303の成績はそれまでのATLの治療成績よりも優れていた。しかしLSG15のコースを重ねるにつれ血球減少が遷延し，再発例の約20%は脳または髄膜病変を伴っていたことから，第3相試験の1アームは

表3 ATLの治療法について推奨されたストラテジー#

抗 HTLV-1 抗体陽性の末梢性 T 細胞腫瘍

↓

病型分類

くすぶり型あるいは予後不良因子を持たない慢性 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 療法または Watch and Wait を考慮。
症候のない患者：Watch and Wait を考慮。

急性型 ATL あるいは予後不良因子を持つ慢性型*

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：VCAP-AMP-VECP（biweekly-CHOP との第 3 相比較試験で評価された）あるいは AZT/IFN（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の骨髄破壊的，または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及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，または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方針をとる。但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 療法は推奨されていない。

#ATL の病型分類に基づいて診断した後に，まず表のように検討し，年齢や臓器予備能を考慮して治療方針を決定する。
（文献 53 より引用）

表4 JCOG-LSG による ATL に対する併用化学療法の臨床試験成績

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

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

LSG15 の治療コース数を 7 から 6 に減じて，髄注に cytarabine を追加した mLSG15（VCAP-AMP-VECP）とし，対照群には JCOG9505 で安全性が確認されており，当時 aggressive NHL の標準的治療法の 1 つとみなされていた biweekly CHOP 療法に髄注を併用した mLSG19 を用いた[60]。この第 3 相比較試験（JCOG9801）は 1998 年より aggressive ATL 患者 118 例において検討された。CR 率と PR 率は，mLSG15 療法で 40%（23/57）と 32%（18/57），mLSG19 療法で 25%（15/61）と 41%（25/61）であり，CR 率は前者で高かった（p=0.020）。さらには 3 年生存率と MST は前者 vs.後者で 23.6%（95% CI: 11.9～35.3%）vs. 12.7%（3.6～21.7%），12.7 ヶ月（9.0～18.8 ヶ月）vs. 10.9 ヶ月（8.4～13.2 ヶ月）であった（片側 p=0.085，ハザード比 0.75；背景因子を調整後の片側 p=0.028，ハザード比 0.63）。Grade 4 の好中球減少，血小板減少，感染症は mLSG15 療法 vs. mLSG19 療法で 98% vs. 83%，74% vs. 17%，7% vs. 3%と前者で高率であり，さらには 3 例の好中球減少に伴う治療関連死（敗

血症2例と間質性肺臓炎1例）を前者で認めた。高悪性度ATLに対するmLSG15は，mLSG19よりも毒性が強いが，良好な生存割合を示したことから，本疾患に対する標準治療としてよいと考えられる[8]。

同種造血幹細胞移植療法

ATLに対する造血幹細胞移植は，これまでの報告からアグレッシブBリンパ腫賭は異なり，自家よりも同種移植が有望とされている[61]。40例の急性型またはリンパ腫型ATLに対するconventionalな骨髄破壊的同種造血幹細胞移植のretrospectiveな解析結果が報告された[62]。移植直前の病状は完全寛解15例，部分寛解13例，不変または病勢進行が12例であった。27例はHLA一致同胞から，5例は不一致同胞から，8例は非血縁HLA一致ドナーからの移植であった。36例のドナーで抗HTLV-1抗体が検索され，うち9例が陽性であった。移植直前の病状が不変または病勢進行であった12例中10例が移植療法後に寛解となったことから，大量化学療法/全身放射線照射による前処置のATLに対する高い抗腫瘍効果が示された。移植後に再発した10例中5例が寛解となったが，うち3例は免疫抑制剤の中止または減量後に寛解となったことから，免疫学的な移植片対ATL効果が強く示唆された。死因の主なものは，移植片対宿主病，感染症，ATLの病勢進行と血栓性微小血管障害であり，治療関連のものが多かった。高率の治療関連死にもかかわらず，推定3年生存率は45%であり，これは低い再発率および前述の再発後の再寛解によると考えられた。

ATLの発症時平均年齢は約60才と高いため，前述の骨髄破壊的前処置法を用いたallo-HSCTを施行可能な症例はATL全体のごく一部である。Allo-HSCTの適応を高齢者や臓器障害を有する症例に対しても拡大する目的で，最近開発された骨髄非破壊的前処置法を用いた同種移植の早期臨床試験がATLに対して現在継続中であり，前述のconventionalな同種移植と同様の40%台の生存率が報告されている[63,64]。ATLに対する骨髄非破壊的移植は有望であるが再発率が高い可能性も指摘されており，さらなる検討が必要である。

1996年から2005年の間に日本でallo-HSCTを受けた386例の調査結果が最近報告された[65]。154例がHLA一致血縁，43例がHLA不一致血縁，99例が非血縁骨髄，90例が臍帯血の移植であった。観察期間中央値41ヶ月（1.5から102ヶ月）で3年生存割合は33%（95% confidence interval，28～38%）であり，多変量解析で予後不良であったのは，50歳以上，男性，完全寛解以外の病状，非血縁骨髄ではなく臍帯血，の4つの因子であった。

以上の有望な成績によってJCOG-LSGでは，非高齢者を対象に化学療法に引き続いてup-frontの骨髄破壊的allo-HSCTの第2相試験を近々開始の予定であり，9801試験での化学療法単独と比較して有用性を検証する。

インターフェロンα（IFN）とジドブジン（AZT）併用療法

1995年に米国から，急性型/リンパ腫型のATL患者19例中11例でIFN/AZT療法が奏効したとNEJM誌に報告された[66]。同号にフランスからも5例（急性型4例とくすぶり型1例）全例で奏効したと報告されたことから，この併用療法の奏効率はすばらしいものではあったが，前治療のないATL患者のMSTは4.8ヶ月とそれまでの日本の臨床試験による化学療法での7～8ヶ月と比べて比較的短かったことから，日本ではこの治療法は検討されてこなかった[67,68]。毒性の主なものは血液毒性であり，その他倦怠感や微熱などIFNでしばしば生じる有害事象が軽度だが認められたが，化学療法，さらには同種移植療法と比べると総じて軽微であった。1994年から2006までに日本を除く多くのHTLV-1 endemic areaからのATL患者209例が後方視的に解析された[69]。そのうち100例がAZT/IFN療法を初回治療として受け，AZTは800～1,000 mg，リコンビナントIFNαは600～900万単位と共に大量が用いられていた。奏効率66%｛CR43%，部分寛解（PR）23%｝であった。MSTと5年全生存率は，初回AZT/IFN療法群では24ヶ月と50%，初回化学療法群では7ヶ月と20%，初回併用群では13ヶ月と8%であった。ATLの病型別の全生存割合の解析では，急性型と慢性型/くすぶり型では併用療法が化学療法より上回っていたが，リンパ腫型では逆に化学療法が上回る傾向であった。併用療法でCRに導入されると急性型でも長期生存が得られると報告されている。注目すべき点としては，慢性型/くすぶり型では観察期間中央値6年（1～13年）での16例の全生存割合が100%であったことである。彼らの報告では急性型に対する化学療法でのMSTはわずか8ヶ月と日本からのVCAP-AMP-VECP療法による13ヶ月と比べて不良であったことから，急性型に対するAZT/IFN療法と化学療法の有用性の比較は現時点では困難である。一方前述したように低悪性度ATLに対する日本でのwatchful waitingによる長期予後は不良であったことから，この病型に対するAZT/IFN療法の成績は皮膚病変の改善と急性転化の防止に有望である[36]。表3に示すようにコンセンサスレポートではATLに対して低悪性度症状の有無により推奨治療を示したが，そのエビデンスレベルは低い[53]。両治療法のうちいずれが勝るかを検証するためにJCOG-LSGでは，予後不良因子のない慢性型と症候を有するくすぶり型ATLを対象にランダム化比較試験

を計画中である。

新規治療法開発

ATLを含むT細胞リンパ腫に対する抗体医薬ほかの新薬の開発が最近進んでいる。ケモカイン受容体のCCR4は制御性T細胞ほかに発現し，ATLの90%以上と末梢性T細胞リンパ腫（PTCL）非特定型の約30%の症例で陽性であり，予後不良因子と報告されている[33]。defucosylate化によりADCC活性を高めた抗CCR4ヒト化MoAb（KW-0761）が日本で開発され，CCR4陽性の再発T細胞腫瘍を対象に第1相試験が行われた[70]。ATL13例，その他のTリンパ腫3例を対象に増量が検討され，毒性は許容範囲であり，予定していた最大投与量が最大耐用量となった。奏効割合は31%（ATLでも31%）と有望であり，特に末梢血病変によく奏効した。この有望な成績を受けて，KW-0761の至適用量とみなされた1.0 mg/kgによる再発・難治の高悪性度ATLに対する第2相試験が開始され，登録は速やかに終了した。再発・難治PTCLに対する単剤の第2相試験と初発の高悪性度ATLに対する化学療法との併用療法の第2相試験が計画されている。その他日本でATLを対象に開発中あるいは検討中の新規薬剤としては，Tリンパ球で重要なプリン・サルベージ酵素であるpurine nucleoside phosphorylaseの阻害剤forodesine，作用機序は多様とされるが骨髄腫，MDSほかで有用性が示されたimmunomoduratory drugのlenalidomide，再発難治の末梢性T細胞リンパ腫に初めて米国FDAにより承認された薬剤である新規葉酸拮抗薬のpralatrexate，再発難治のCTCLに同じく承認されているヒストン脱アセチル化酵素阻害剤のromidepsineなどがある。

おわりに

HTLV-1が病因ウイルスであるATLについては，疾患の発見から約30年を経て多くの知見が得られ，HTLV-1の感染予防も可能となった。しかし，化学療法や同種移植療法によりATL症例の一部に長期生存がもたらされるようになった現在でもATLの標準的治療法は確立しておらず，HTLV-1キャリアにおけるATL発症予防法は全く開発されていない。今後は化学療法と移植療法のみならず，トランスレーショナルリサーチによるATL発症のkeyとなる可能性のある遺伝子の同定およびその遺伝子を標的とした発症予防法や治療法の開発が，よくデザインされた臨床試験により行われることが望まれる。

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Clinical Trials for Human T-Cell Lymphotropic Virus Type I–Associated Peripheral T-Cell Lymphoma in Japan

Kensei Tobinai

The most common subtype of T-/natural killer (NK) cell lymphoma in Japan is adult T-cell leukemia-lymphoma (ATL), which is associated with the human T-cell lymphotropic virus type I (HTLV-1). The investigators in Japan have conducted several clinical trials on multi-agent chemotherapy and stem cell transplantation for patients with ATL. They have also initiated several new clinical trials with a number of agents: an anti-CCR4 antibody, KW-0761; forodesine, a purine nucleoside phosphorylase inhibitor; and lenalidomide, an immunomodulatory agent. Clinical trials with pralatrexate, a folate analog, and denileukin diftitox, an immunoconjugate, are under discussion for patients with ATL and peripheral T-cell lymphoma (PTCL).
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EPIDEMIOLOGY OF T-CELL LYMPHOMA IN JAPAN

After the publication of the World Health Organization (WHO) classification third version, hematopathologists in Japan reviewed more than 3,000 Japanese cases of malignant lymphomas.[1] They found that nearly 70% of patients had B-cell lymphoma and that 25% had T-/natural killer (NK) cell lymphoma. The most common subtype of T-/NK cell lymphoma in Japan was adult T-cell leukemia-lymphoma (ATL), found in 7.5% of patients. In Kyushu, a southwestern island of Japan and an area in which human T-cell lymphotropic virus type I (HTLV-1) is highly endemic, nearly 20% of malignant lymphomas are ATLs (Table 1).

Acute-type ATL has characteristic clinical findings, including flower cells with hyperlobulated nuclei in peripheral blood, hypercalcemia, and frequent multiple organ involvement, such as skin, gastrointestinal tract, lung, and central nervous system. Leukemic cells of ATL have a peripheral T-cell phenotype: $CD4^+$, $CD8^-$, and $CD25^+$. Recent investigation indicates that ATL tumor cells derive from regulatory T cells. Clinically, the presence of antibodies to HTLV-1 in serum is important to make a diagnosis of ATL. Based on clinical features, it is possible to classify ATLs into four clinical subtypes: acute, lymphoma, chronic, and smoldering types. Survival rates vary with each clinical subtype.[2] ATL is also an immune-suppressed disease. Consequently, frequent complications include opportunistic infections, such as *Pneumocystis jiroveci* and fungal or viral infections. In Japan, there are about 1.2 million HTLV-1 carriers, and approximately 700 to 1,000 virus carriers develop ATL each year.

HTLV-1 is an RNA retrovirus that has a unique structure called *pX*, near the 3′ long terminal repeat. In the *pX* region, *tax* gene encodes Tax protein, which causes transcriptional activation of viral genes. In addition, Tax interacts with many cellular proteins and promotes proliferation and inhibits apoptosis.

HTLV-1 is not as easily transmissible as other viruses, such as human immunodeficiency virus or hepatitis B or C viruses. The most common transmission route of HTLV-1 is breast milk. Sexual transmission can occur, usually from male to female, and blood transfusion can also cause transmission of this virus. Since 1987, blood screening for HTLV-1 serum antibodies has been conducted in Japan for all blood donors, and no apparent cases of transmission have occurred by blood transfusion since that date. Due to Tax and other virus-encoded genes and proteins, proliferation of $CD4^+$ T cells occurs, and sometimes Tax is inhibited by immune mechanisms. After a long latency period, 50 to 60 years in most cases, a fraction of virus carriers develops ATL.

National Cancer Center Hospital, Tokyo, Japan.
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Address correspondence to Kensei Tobinai, MD, PhD, National Cancer Center Hospital, 5-1-1 Tsukiji, Chou-ku, Tokyo, Japan 104-0045. E-mail: ktobinai@ncc.go.jp
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Table 1. Major Subtypes of T- or NK Cell Non-Hodgkin Lymphoma in Japan[1]

Subtype	Percent
Adult T-cell leukemia-lymphoma	7.5%
• in Kyushu only	19.2%
PTCL, unspecified	6.7%
Nasal and nasal-type NK/T-cell lymphoma	2.6%
Angioimmunoblastic T-cell lymphoma	2.4%
Anaplastic large cell lymphoma	1.5%

Abbreviations: NK, natural killer; PTCL, peripheral T-cell lymphoma.

CLINICAL TRIALS FOR ATL IN JAPAN

The Japan Clinical Oncology Group (JCOG) has conducted five clinical trials for ATL and aggressive lymphoma including ATL since the early 1980s (Table 2). In the earlier two trials, JCOG8101 and 8701 using CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like regimens, JCOG enrolled ATL patients into aggressive lymphoma protocols. ATL patients' median survival time was only 8 months versus 44 months for non-ATL patients.

In the early 1990s, JCOG initiated clinical trials specifically targeting ATL. JCOG 9109 was a phase II study with a pentostatin-containing chemotherapy regimen,[3] but there was no improvement in results.

JCOG9303[4] evaluated a dose-intensified multi-agent regimen incorporating MDR1/P-glycoprotein-unrelated agents, such as nitrosourea and platinum compounds. The regimen consisted of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone). Patients also received granulocyte colony-stimulating factor (G-CSF) support. Overall survival (OS) in this trial was 31% at 2 years, and median survival time was 13 months. Based on the findings that untreated ATL cells express MDR1/P-glycoprotein intrinsically, CHOP regimens may not be effective for this disease. The median survival appeared to be improved with this regimen compared to historical controls with CHOP-like regimens (13 months *v* 7–8 months).

JCOG9801 was the first phase III trial to specifically target untreated aggressive ATL.[5] This trial compared a biweekly CHOP-like regimen, which included intrathecal methotrexate and cytatabine, to the VCAP-AMP-VECP regimen used in JCOG 9303. Three-year OS rates were 24% and 13% on the VCAP-AMP-VECP regimen and the CHOP-like regimen, respectively, but the results were not statistically significant (P .085). After adjustment for some prognostic factors, including bulky tumor mass, the difference reached statistical significance (P .029). Based on this study, JCOG concluded that the dose-intensified regimen should be the basis for future investigation in the treatment of ATL.

Medical therapies are not curative in most patients with ATL, but allogeneic stem cell transplantation with conventional conditioning has been shown to provide sustained survival for ATL patients, with a 3-year OS of 45%.[6] Based on the promising results of allogeneic stem cell transplant in retrospective analyses, JCOG will initiate JCOG0907, a phase II study of VCAP-AMP-VECP followed by allogeneic stem cell transplant for untreated patients with aggressive ATL.

NEW AGENT DEVELOPMENT FOR ATL

ATL cells express chemokine receptor-4 (CCR4) in 90% of ATL patients,[7] which can be confirmed by flow cytometry or by immunohistochemistry assays. A humanized anti-CCR4 antibody, KW-0761, has been developed by a Japanese pharmaceutical company. Using defucosylation technology, antibody-dependent cell-mediated cytotoxicity activity is accentuated nearly 100-fold.

The phase I clinical trial of this antibody has recently been completed.[8] Sixteen patients, 13 patients with ATL and three with peripheral T-cell lymphoma (PTCL), were administered KW-0761 intravenously weekly for a total of four doses. The study had four dose cohorts: 0.01 mg/kg, 0.1 mg/kg, 0.5 mg/kg, and 1.0 mg/kg. One of six patients treated at the 1.0-mg/kg level developed dose-limiting toxicities after the fourth dosing, possibly related to KW-0761 treatment. KW-0761 was well tolerated at all of the dose levels tested. The overall response rate was 31% (four of 13 patients), including two complete responses and two partial responses. An additional four patients had stable disease. A subsequent phase II study of KW-0761 for relapsed ATL using 8 weekly infusions at 1.0 mg/kg is ongoing. Another phase II study of KW-0761 in combination with chemotherapy for untreated ATL will be initiated soon.

Forodesine (BCX-1777), a purine nucleoside phosphorylase inhibitor, has also been used in clinical trials

Table 2. Japan Clinical Oncology Group Trials for ATL

Study	N	% CR	MST (mo)	% OS
JCOG8101	54	28	7.5	8 (4 yr)
JCOG8701	43	42	8.0	12 (4 yr)
JCOG9109	60	28	7.4	16 (2 yr)
JCOG9303	93	35	13	31 (2 yr)
JCOG9801	118	32	11	24 (2 yr)

Abbreviations: CR, complete response; JCOG, Japan Clinical Oncology Group; MST, median survival time; OS, overall survival.

for T-cell lymphoma. This agent has clinical efficacy in T-cell acute lymphoblastic leukemia and cutaneous T-cell lymphoma (CTCL). A phase I study for PTCL and ATL patients will soon be completed, and subsequent phase II studies for ATL and PTCL are in preparation.

The immunomodulatory agent lenalidomide has activity in a variety of hematologic malignancies, including myeloma and aggressive and indolent B-cell non-Hodgkin lymphoma. A group at Northwestern University conducted a phase II study with lenalidomide in eight evaluable CTCL patients.[9] The preliminary objective response rate was 38%. The toxicity profile was manageable. A phase I study of lenalidomide for ATL patients is now in preparation in Japan.

Clinical trials with other agents are in varying stages of preparation. A phase I trial of vorinostat, a histone deacetylase inhibitor, was completed in CTCL patients to obtain a license for CTCL in Japan. Clinical trials with pralatrexate, a folate analog, and denileukin diftitox, an immunoconjugate, are under discussion for patients with PTCL.

CONCLUSIONS

Although the majority of patients with ATL are still incurable with the current treatment modalities, it is expected that the investigations on novel agents and stem cell transplantation will improve outcomes for these patients in the near future.

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EXPERT REVIEWS

Adult T-cell leukemia–lymphoma: current treatment strategies and novel immunological approaches

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Ryuji Tanosaki[†1] and Kensei Tobinai[2]

[1]*Pathology and Clinical Laboratory Medicine Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan*
[2]*Hematology and Stem Cell Transplantation Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan*
[†]*Author for correspondence:*
Tel.: +81 335 422 511 ext. 7066
Fax: +81 335 423 815
rtanosak@ncc.go.jp

Adult T-cell leukemia–lymphoma (ATL) is a peripheral T-cell malignancy, closely associated with human T-cell lymphotropic virus type I infection. Clinically, ATL is classified into four subtypes: acute, lymphoma, chronic and smoldering type. Although the prognosis of chronic and smoldering-type ATL is relatively good, that of patients with acute- or lymphoma-type ATL still remains extremely poor. Zidovudine/IFN-α therapy seems to be promising, although its efficacy has not yet been confirmed in well-designed prospective studies. High-dose chemotherapy with the support of autologous transplantation does not improve outcome. Allogeneic stem cell transplantation is promising and approximately 40% of aggressive ATL patients are expected to survive long-term, although transplantation-related mortality is as high as 40–50%. Stem cell transplantation using reduced-intensity conditioning is also effective and safer, with graft-versus-ATL and graft-versus-human T-cell lymphotropic virus type I effects observed after transplantation. Novel approaches including new agents such as purine nucleoside phosphorylase inhibitors and histone deacetylase inhibitors, or targeted immunotherapy using antichemokine receptor-4 antibody or dendritic cell/peptide vaccine are also warranted.

KEYWORDS: adult T-cell leukemia–lymphoma • graft-versus-ATL effects • graft-versus-HTLV-1 effects • hematopoietic stem cell transplantation • human T-cell lymphotropic virus type I • IFN-α • reduced-intensity stem cell transplantation • treatment • zidovudine

Adult T-cell leukemia–lymphoma (ATL) is a peripheral T-cell malignancy associated with human T-cell lymphotropic virus type I (HTLV-1) infection that develops after a very long latency period [1]. Leukemia is preceded by oligoclonal expansions arising from a polyclonal background of activated HTLV-1-infected T cells as a result of the expression of the viral trans-activator protein Tax, which activates various cellular genes [2,3] and creates an autocrine loop involving IL-2, IL-15 and their cognate receptors. Clinically, ATL is classified into four subtypes: acute, lymphoma, chronic and smoldering types. Patients with aggressive ATL, either acute or lymphoma type, generally have a poor prognosis because of intrinsic chemoresistance of the malignant cells, a large tumor burden frequently associated with multiorgan failure, hypercalcemia and/or frequent infectious complications due to profound T-cell immune deficiency [4]. Chemoresistance is considered to be due to multiple factors, including overexpression of the multidrug resistance protein, *TP53* mutations and dysregulation of various cellular oncogenes in ATL cells [5]. On the other hand, patients with indolent ATL, either chronic or smoldering type, have a better prognosis.

Following the *13th International Conference on Human Retrovirology* in Hakone, Japan, in 2007, a proposal was made by an international consensus meeting for the definition, prognostic factors, treatments and response criteria [6]. According to this proposal, the diagnosis and the subclassification of ATL should be based on the WHO classification [7] and Shimoyama's criteria [8], respectively (TABLE 1). To make decisions regarding treatment, ATL is first divided into two groups: indolent and aggressive ATL. Indolent ATL consists of smoldering and 'favorable' chronic-type, and aggressive ATL consists of acute, lymphoma and 'unfavorable' chronic-type. Three risk factors (blood urea nitrogen > normal upper limit, lactate dehydrogenase > normal upper limit and serum albumin < normal lower limit) have been

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

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte ($\times 10^3$/μl)	<4	□4[†]	<4	[‡]
Abnormal T lymphocytes	□5%[§]	+[¶]	□1%	+
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	[‡]	[‡]	[‡]
CNS	No	[‡]	[‡]	[‡]
Bone	No	No	[‡]	[‡]
Ascites	No	No	[‡]	[‡]
Pleural effusion	No	No	[‡]	[‡]
GI tract	No	No	[‡]	[‡]

[†]Accompanied by T lymphocytosis (3.5 × 10^3/μl or more).
[‡]No essential qualification except terms required for other subtype(s).
[§]Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood.
[¶]If abnormal T lymphocytes are less than 5% in peripheral blood, histologically proven tumor lesion is required.
[#]Typical 'flower cells' may be seen occasionally.
+: Positive; HTLV-I: Human T-lymphotropic virus type I; LDH: Lactate dehydrogenase; mEq: Milliequivalents; N: Normal upper limit.
Data from [8].

identified by the Japan Clinical Oncology Group (JCOG) that indicate a patient with unfavorable chronic-type ATL, whose prognosis is as poor as other aggressive ATLs [9].

The treatment strategies for ATL vary between different countries. In 1995, two reports described the efficacy of zidovudine/IFN-α (AZT/IFN-α) therapy for the first time [10,11]. The overall response rate was 67% (16 out of 24 patients), but the median survival time in previously untreated ATL patients was only 4.8 months, shorter than that of patients treated with chemotherapy in Japan. The complete response (CR) rate was 25% in untreated ATL patients, which was as low as the rate in patients treated with chemotherapy. However, these drugs have not been available for treating ATL patients by the national health insurance system in Japan; thus, AZT/IFN-α therapy has not been extensively investigated in Japan and very few experiences with the use of AZT/IFN-α therapy are available. By contrast, AZT/IFN-α therapy has been the treatment of choice in practical settings in the USA, England, France and Brazil.

Despite this background, treatment strategies should be based on the ATL subclassification and prognostic factors at onset, as well as the response to initial therapy. The prognostic factors include clinical factors, such as performance status (PS), lactate dehydrogenase, age, number of involved lesions and hypercalcemia and molecular factors, such as Ki-67 expression, alteration of p53 or p15INK4B/p16INK4A and overexpression of interferon regulatory factor 4 [6].

Treatment of smoldering- or chronic-type ATL

According to a previous nationwide study in Japanese patients with ATL, the 4-year survival rate for acute-, lymphoma-, chronic- and smoldering-type ATL is 5.0, 5.7, 26.9 and 62.8%, respectively [8]. Therefore, the prognosis of patients with smoldering and chronic-type ATL has been considered to be relatively good. Because the majority of patients are elderly and some of them have infectious or other complications, the main treatment option for these indolent-type ATL patients has been to watch and wait. However, a recent report concerning long-term follow-up of 90 patients with indolent ATL revealed that the prognosis of patients with smoldering- or chronic-type ATL is poorer than previously expected. The median survival time was 4.1 years; 12 patients remained alive for more than 10 years, 44 progressed to acute-type ATL and 63 patients died. Most patients were followed up with a 'watchful waiting' approach and 12 patients were treated with chemotherapy. The estimated 5-, 10- and 15-year survival rates were 47.2, 25.4 and 14.1%, respectively, with no plateau in the survival curve [12]. Another report of long-term follow-up of smoldering-type ATL patients in the Kyushu district of southwestern Japan, which is the most endemic area of HTLV-1 and ATL worldwide, disclosed that 14 (54%) out of 26 patients remained alive without progression, with a median follow-up of 7 years (range: 6.5–15 years), and that the estimated risk of transformation to overt ATL ranged from 20 to 42%, with a median follow-up of 6.5 years. As the majority of smoldering-type ATL patients were diagnosed by chance during a regular physical check-up or clinical visit because of other reasons than ATL-related symptoms, and were generally asymptomatic, many patients did not return to the clinics where they were diagnosed; and 53 (67%) out of 79 patients were ineligible in this survey because of missing or inappropriate information or being lost to follow-up. Thus, it is difficult to precisely estimate the long-term prognosis in this group of ATL patients [13].

On the other hand, a recent report from outside Japan on meta-analysis suggests that AZT/IFN-α treatment is promising. All 17 patients with smoldering- or chronic-type ATL who

were treated with antiviral therapy only involving AZT/IFN-α survived beyond 5 years, whereas the 5-year survival of patients with the same subtypes who were treated by other means was 42% [14]. In order to prove the efficacy of AZT/IFN-α treatment, randomized prospective studies are warranted.

Treatment of lymphoma- or acute-type ATL

For aggressive-type ATL patients, physicians in Japan appear to follow considerably different treatment strategies from those in Western countries; multidrug chemotherapy and/or allogeneic hematopoietic stem cell transplantation (SCT) are currently chosen for most patients in Japan, whereas AZT/IFN-α with or without chemotherapy might be used more often in Western countries. Since the early 1980s, JCOG has conducted five prospective clinical trials [15]. In the earlier two trials, JCOG 8101 and 8701 using cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like regimens, ATL patients were enrolled into the same protocol as aggressive lymphoma patients. The median survival time was only 8 months in ATL patients compared with 44 months in non-ATL patients. In the early 1990s, JCOG initiated clinical trials specifically targeting ATL. A Phase II study of chemotherapy including pentostatin (JCOG 9109) showed no improvement in the median survival time [16]. In the next clinical trial (JCOG 9303), a dose-intensified multiagent regimen was tested by incorporating MDR1/P-glycoprotein-unrelated agents, such as nitrosourea and platinum compounds and granulocyte colony-stimulating factor [17]. The regimen consisted of vincristine, cyclophosphamide, doxorubicin and prednisone (VCAP), doxorubicin, ranimustine and prednisone (AMP), and vindesine, etoposide, carboplatin and prednisone (VECP). The 2-year overall survival rate and median survival time were 31% and 13 months, respectively, which appeared to be an improvement compared with historical controls treated with CHOP-like regimens.

The first Phase III trial (JCOG 9801) specifically targeting ATL compared six courses of the VCAP–AMP–VECP (LSG15) regimen used in JCOG 9303 to eight courses of a biweekly CHOP-like regimen [18]. A total of 118 patients were assigned to either treatment arm. The CR rate was higher in the LSG15 arm than in the CHOP arm (40 vs 25%; p = 0.020). The median progression-free survival time and rate at 1 year were 7.0 months and 28% in the VCAP–AMP–VECP arm and 5.4 months and 16% in the biweekly CHOP arm, respectively (p = 0.100; two-sided p = 0.200; hazard ratio: 0.77; 95% CI: 0.52–1.14). The overall survival (OS) at 3 years was 24% in the LSG15 arm and 13% in the CHOP arm (p = 0.085; two-sided p = 0.169), although three toxic deaths occurred in the LSG15 arm (Figure 1). According to Cox regression analysis on OS, the hazard ratio for the treatment arms was 0.62 (95% CI: 0.38–1.01; p = 0.028; two-sided p = 0.056). The higher 3-year survival rate and CR rate with LSG15 compared with biweekly CHOP suggests that LSG15 is more effective; therefore, it is currently the recommended chemotherapy regimen.

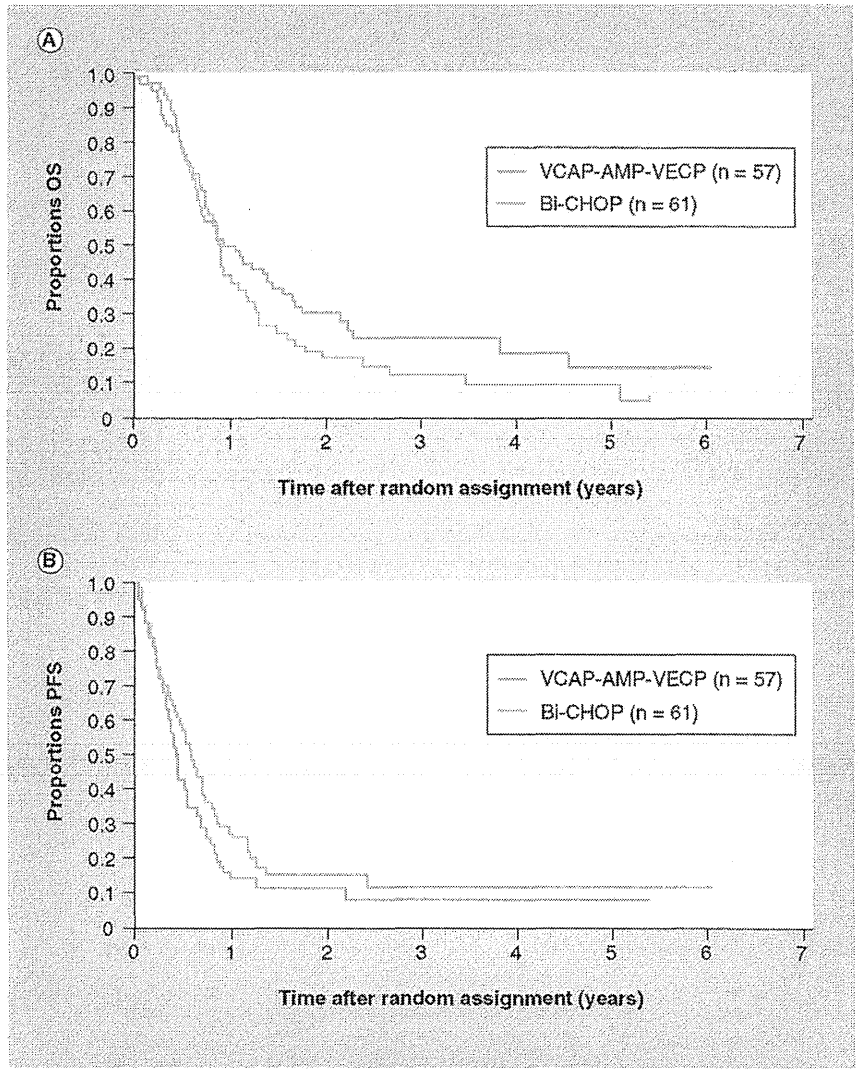

Figure 1. Kaplan–Meier estimate of (A) overall survival and (B) progression-free survival for all randomly assigned patients.
AMP: Doxorubicin, ranimustine and prednisone; Bi-CHOP: Biweekly cyclophosphamide, doxorubicin, vincristine and prednisone; OS: Overall survival; PFS: Progression-free survival; VCAP: Vincrisitine, cyclophosphamide, doxorubicin and prednisone; VECP: Vindesine, etoposide, carboplatin and prednisone.
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Only a few reports have addressed high-dose chemoradiotherapy with the support of autologous SCT. According to a review of the literature describing a total of eight ATL patients who underwent autologous SCT [19], all patients with ATL who underwent autologous SCT relapsed or died due to transplant-related toxicity, irrespective of subtype or disease status, stem cell source, conditioning regimen or whether it involved *ex vivo* manipulation. The authors concluded that autologous SCT appeared to provide little benefit for ATL in contrast to non-ATL lymphomas.

Zidovudine/IFN-α therapy has been performed outside Japan. According to a recent worldwide meta-analysis of 254 patients treated from 1995 to 2008, the median survival for 98 patients with acute-type ATL who received first-line AZT/IFN-α therapy (n = 45) or chemotherapy (n = 53) was 9 and 6 months, respectively. However, achieving a CR with first-line AZT/IFN-α therapy resulted in 82% 5-year survival (n = 11). On the other hand, the median survival of 84 patients with lymphoma-type ATL who were treated with first-line AZT/IFN-α therapy (n = 13) or chemotherapy (n = 71) was 7 and 16 months, respectively; this type of ATL does not benefit from AZT/IFN-α treatment [14]. These data suggest that first-line AZT/IFN-α therapy results in prolonged survival in acute-type ATL who have achieved CR, but not lymphoma-type ATL patients. As has been mentioned before, there have been very few experiences with AZT/IFN-α therapy in Japan, which is the most endemic area for ATL and HTLV-1 infection; therefore, the treatment should also be investigated there.

Allogeneic SCT in ATL

Accumulating evidence suggests the potent efficacy of allogeneic SCT in aggressive-type ATL. The first reported case of allogeneic SCT was bone marrow transplantation from an HLA-matched sibling donor [20] and it was followed by a few case reports [21–24]. In 1994, a case of donor-origin ATL relapse was molecularly confirmed following allogeneic SCT [21]. However, only one case of donor-derived relapse has appeared since then [25]. Although the transmission of HTLV-1 from infected host cells to transplanted donor cells via cell-to-cell contact is speculated to occur after allogeneic SCT, especially in reduced-intensity stem cell transplantation (RIST), it might not cause the development of ATL in most cases.

In 2001, Utsunomiya *et al.* first indicated improved outcome by reviewing ten patients from nine institutions [26]. The study showed a plateau in the progression-free survival curve, with a median of 17.5 months. In 2007, the data were updated for the same cohort with a median follow-up of 9 years; four patients were still alive and the estimated 10-year overall survival was 40% [27]. Several subsequent retrospective surveys confirmed that approximately 40% of patients survive without disease. However, the studies also indicate that treatment-related mortality is as high as 40%, despite the fact that most patients who undergo allogeneic SCT are less than 50 years of age, which is younger than the majority of ATL patients [28–30]. A nationwide retrospective survey of allogeneic SCT in 386 patients with ATL in Japan was recently reported. The 3-year overall survival rate for the entire cohort was 33% (Figure 2) and a multivariable analysis revealed four recipient factors significantly associated with lower survival rates: older age (>50 years), male sex, status other than complete remission and the use of unrelated cord blood compared with the use of HLA-matched related grafts. Of 333 patients who survived 30 days after transplantation, 136 patients experienced a relapse or progression of ATL at a median of 76 days (range: 1–1964 days) after transplantation (Figure 3). Of a total 376 evaluable patients, 161 (43%) died due to treatment-related mortality, with major causes of death being infection (32%) and organ failure (33%) [31]. This very high mortality rate is almost similar to previous reports and definitely shows that allogeneic SCT is effective but very toxic, especially in ATL patients, although a substantial proportion of ATL patients could survive for a long time after allogeneic SCT. Notably, the majority of patients were elderly and only a third of aggressive ATL patients are estimated to be eligible for standard allogeneic SCT due to age.

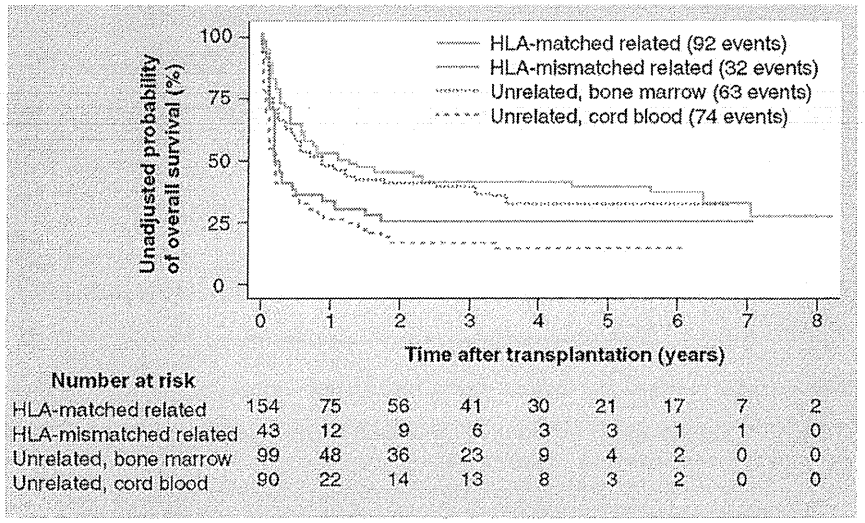

Figure 2. Unadjusted Kaplan–Meier estimates of overall survival stratified according to type of graft source.
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Therefore, we were encouraged to apply reduced-intensity conditioning to allogeneic SCT in patients with ATL, and the ATL-RIST Study Group was organized in Japan with grant support for Cancer Research by the Ministry of Health, Labor and Welfare. The rationale was as follows: first, the fact that a population of ATL patients who underwent allogeneic SCT, not autologous SCT, survived for a long time without disease indicating that a graft-versus-ATL effect could be expected after allogeneic SCT. Second, most ATL patients are not eligible for conventional allogeneic SCT, as the onset of ATL is after 50 years of age and the transplantation-related mortality rate is

extremely high. Therefore, a less toxic allogeneic SCT technique should be applied. We first conducted a Phase I study to determine safety and efficacy, and the primary end points were engraftment and the overall survival rate on day 100 after transplantation [32]. Patient eligibility was acute- or lymphoma-type, CR or partial response (PR) and PS 0–1. The conditioning regimen consisted of fludarabine, busulfan and rabbit anti-T-lymphocyte globulin (ATG).

The first study enrolled 15 patients and confirmed feasibility and safety of the technique, but nine patients (60%) relapsed, seven within 100 days [32]. This high rate of early relapse raised the possibility that ATG might have suppressed the graft-versus-ATL effect. Therefore, ATG was eliminated from the conditioning regimen and the study was repeated in an additional 14 patients. However, no significant differences were observed between the patients with or without ATG with regards to OS or relapse rate. In a total of 29 patients, a third survived long term without disease, a quarter died from transplantation and half of the patients relapsed early after transplantation [33].

Notably, some patients who had relapsed after allogeneic SCT responded to the cessation or withdrawal of immune suppressants and there are some long-term survivors currently without disease. Furthermore, the development of grade I–II acute graft-versus-host disease (GVHD) was significantly positively affected with respect to overall and progression-free survival compared with patients who developed no or grade III–IV acute GVHD in the two Phase I studies already described (Figure 4) [33]. Considering the refractoriness of ATL, these facts suggest that graft-versus-ATL effects could be expected after transplantation. Furthermore, the HTLV-1 copy number decreased dramatically below the carrier level after transplantation in most long-term survivors. This finding suggests the existence of a graft-versus-HTLV-1 effect.

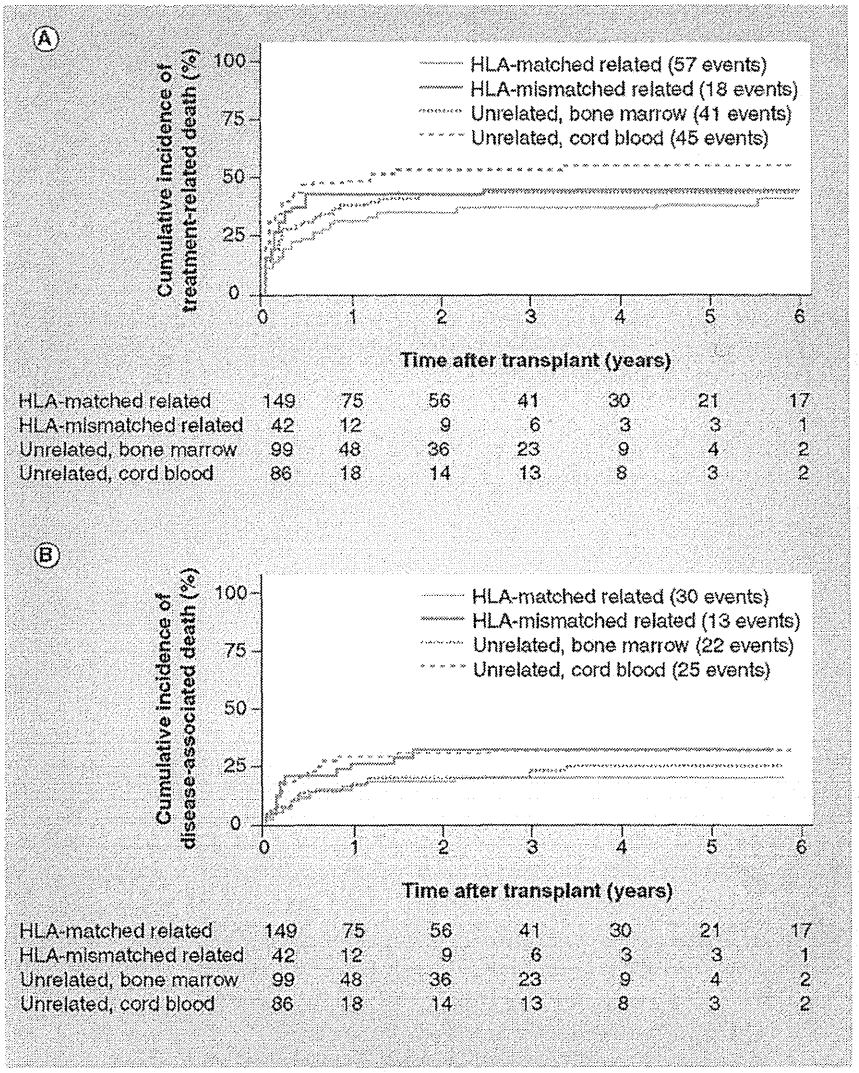

Figure 3. Unadjusted cumulative incidence of (A) treatment-related mortality and (B) disease-associated mortality according to the type of graft source after allogeneic hematopoietic stem cell transplantation in patients with adult T-cell leukemia.

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New agents & monoclonal antibody in the treatment of ATL

Several new agents are currently being developed. Forodesine (BCX-1777), a purine nucleoside phosphorylase inhibitor, is being tested in clinical trials for T-cell lymphoma. This agent shows clinical responses in T-cell acute lymphoblastic leukemia and cutaneous T-cell lymphoma (CTCL). A Phase I study for peripheral T-cell lymphoma (PTCL), including ATL patients, will soon be completed [15]. Bortezomib, which inhibits the proteasome, thereby inhibiting activation of NF-□B, is now widely used for relapsed or refractory multiple myeloma. This agent induces cell death in HTLV-1-associated cell lines and in ATL cells *in vitro* via multiple pathways, including NF-□B inhibition [34]. The immunomodulatory agent lenalidomide, which is active in a variety of hematological malignancies, including myeloma and B-cell lymphomas, will also be tested in the near future in a Phase I study in Japan. Other agents being considered for clinical trials in ATL patients include histone deacetylase (HDAC) inhibitors, such as vorinostat, and folate analogs, such as pralatrexate.

Therapy using monoclonal antibodies is based on the unique phenotypic characteristics of ATL cells [35]; they are $CD4^+$ T cells that strongly express the IL-2 receptor (IL-2R; CD25,

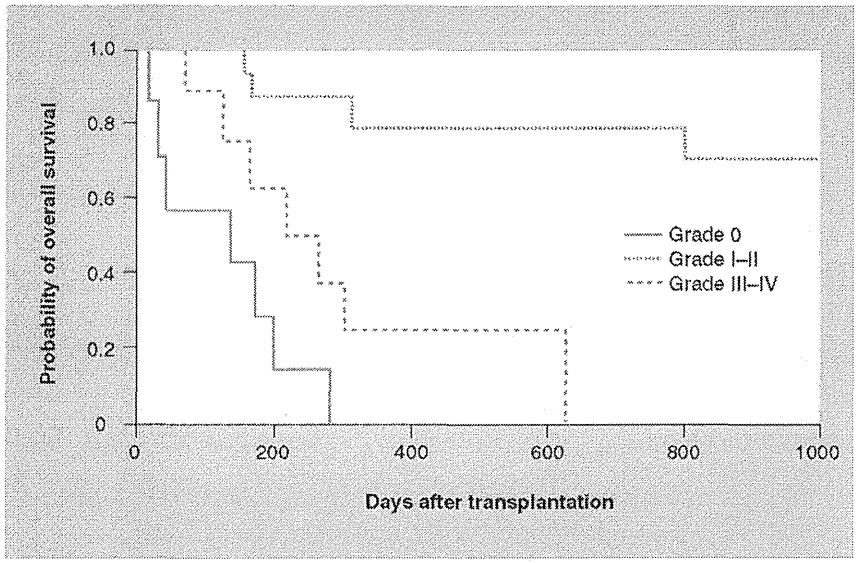

Figure 4. Kaplan–Meier estimate of overall survival for all patients according to the grade of acute graft-versus host disease. Patients with grade I–II acute graft-versus-host disease (GVHD) had significantly better overall survival compared with those without acute GVHD ($p = 0.0012$). Severe acute GVHD (grade III–IV) was not favorably affected in respect to overall survival compared with those without acute GVHD ($p = 0.39$).
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Tac) and are positive for CD3 and other mature T-cell antigens (e.g., CD2, CD5, CD52 and CCR4) but lack CD7. Because the strong expression of IL-2R is unique from many other PTCLs, monoclonal antibodies targeting the IL-2 receptor (anti-Tac), either radiolabeled or unlabelled (daclizumab), have been evaluated, particularly in relapsed or refractory ATL patients.

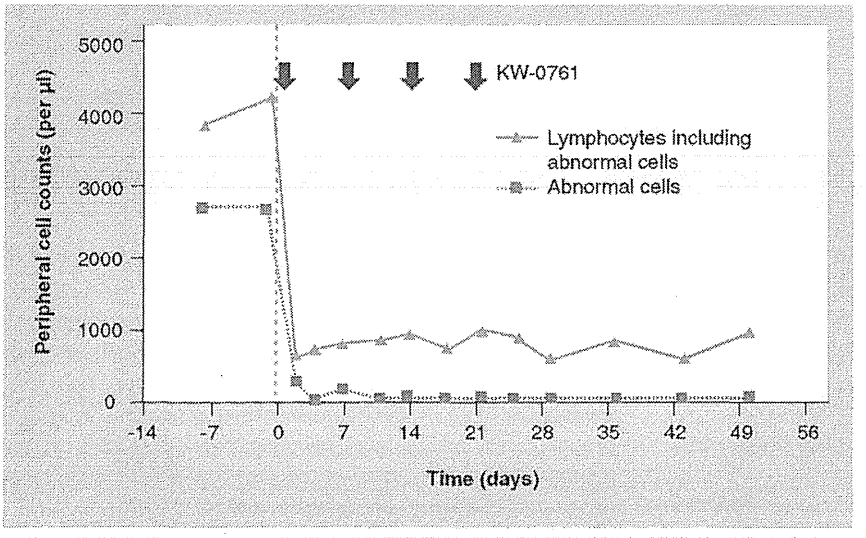

Figure 5. Response to humanized defucosylated anti-CCR4 antibody (KW-0761) in a representative patient with acute-type adult T-cell leukemia–lymphoma. The time course of lymphocytes and adult T-cell leukemia–lymphoma cells in the peripheral blood after treatment (arrows) with 0.1 mg/kg KW-0761 is shown.
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However, efficacy is unlikely owing to the very low complete remission rate [36–38]. Denileukin diftitox (Ontak® [Eisai Co. Ltd., Tokyo, Japan]), an engineered protein combining IL-2 and diphtheria toxin, is used mostly for CTCL in the USA [39,40], but is also being discussed for CD25+ PTCL patients in Japan. Anti-CD2 monoclonal antibody (siplizumab) [41], anti-CD52 antibody (alemtuzumab, Campath 1H) [42–44], anti-CD4 antibody (zonolimumab) [45] and antitransferrin receptor antibody [46] are also in development, but data are currently limited. As the chemokine receptor (CCR)4 is expressed on the leukemia cells in 90% of ATL patients, a humanized defucosylated anti-CCR4 antibody (KW-0761) was recently developed. The Phase I study has revealed promising results [47]. A total of 16 patients with PTCL, including 13 ATL patients, received KW-0761 once a week for 4 weeks by intravenous infusion. Doses were escalated from 0.01 to 1.0 mg/kg at four levels by a three-plus-three design. Overall, 15 patients completed the protocol treatment. Only one patient at the 1.0 mg/kg dose level developed grade 3 dose-limiting toxicities, skin rash, febrile neutropenia and grade 4 neutropenia. Lymphopenia ($n = 10$) was the most often observed grade 3–4 treatment-related toxicity and the maximum tolerated dose was not reached. Therefore, the recommended Phase II dose was determined to be 1.0 mg/kg. Five patients (31%; 95% CI: 11–59%) achieved objective responses: two CR and three PR. The two patients achieving CR had acute-type ATL and their CR status was maintained until the last follow-up (12 and 3 months) without subsequent therapy. The median progression-free survival was 46 days, though some patients remained progression free at last follow-up. A clinical response was observed even at 0.01 mg/kg and tumor cells disappeared from the peripheral blood rapidly after KW-0761 infusion in most patients (Figure 5) [47]. The Phase II study of KW-0761 for relapsed or refractory ATL patients is currently underway in Japan.

Novel immunological approach

As suggested by the accumulated experience with allogeneic SCT in ATL patients, ATL cells are highly immunogenic. Several lines of evidence support the idea that a potent graft-versus-ATL

effect is induced after allogeneic SCT. About a third of ATL patients survive without disease after allogeneic SCT with reduced-intensity conditioning [32,33], whereas most patients who undergo high-dose chemoradiotherapy with the support of autologous SCT die of disease [18], which cannot be explained without graft-versus-ATL effects. Some ATL patients who relapse after allogeneic SCT show clinical responses, including complete remission, when immune suppressive agents are rapidly reduced and stopped with or without donor lymphocyte infusion [48,49]. Grade I–II acute GVHD is favorably affected with regards to OS and progression-free survival after allogeneic SCT using reduced-intensity conditioning [33]. All of these observations support the existence of graft-versus-ATL effects after allogeneic SCT.

The HTLV-1 proviral load in the peripheral blood decreases after transplantation and reaches an undetectable level within 6 months in more than half of the patients who undergo RIST, including those who were transplanted from an HTLV-1 carrier donor [33,50]. After HTLV-1 enters a host cell, the viral genomic RNA is reverse transcribed into a double-stranded DNA form and randomly integrated into the host chromosomal DNA. HTLV-1 is widely believed to replicate primarily not as free viral particles, but as a provirus, by inducing the proliferation of infected host cells [3]. Therefore, the fact that HTLV-1 genomic DNA is not detected in many ATL patients undergoing allogeneic SCT indicates that not only ATL leukemic clones, but also polyclonal HTLV-1-infected cells, are eliminated from the peripheral blood after allogeneic SCT. This finding suggests the existence of graft-versus-HTLV-1 effects.

The mechanism underlying the elimination of monoclonally or polyclonally integrated HTLV-1-infected cells after allogeneic SCT remains to be elucidated. HTLV-1 is recognized as a foreign pathogen in infected individuals and an HTLV-1 Tax-specific cytotoxic T-lymphocyte (CTL) response is observed in most carriers [51]. A series of experimental rat models for HTLV-1-infected T-cell lymphoma revealed that potent anti-tumor effects are exerted and mediated by CTL that are predominantly directed at HTLV-1 Tax in immune-competent rats [52]. Although Tax is the main target of the host's CTLs, *Tax* transcripts are detected in only approximately 40% of ATL patients. *Tax* transcripts are considered necessary early after infection to initiate transformation but are not required to maintain the transformed phenotype of ATL cells [3]. HTLV-1 expression has also been found to be inducible in the ATL cells from some ATL patients after several hours of culture. Therefore, HTLV-1 Tax might be expressed in HTLV-1 infected cells *in vivo* and it remains a possibility that it could be the major target of CTLs after allogeneic SCT [53].

Although there have been controversies concerning the possible target molecules associated with graft-versus-ATL and HTLV-1 effects, a Phase I study of dendritic cell (DC) therapy, conducted by the ATL-RIST Study Group, was recently started in Japan. In this study, monocyte-derived DCs loaded with HLA-A2 or A24-restricted HTLV-1 Tax peptide will be infused into ATL patients with the corresponding HLA phenotype. The study is also designed to monitor HLA A2- and A24-restricted CTLs using specific tetramers, as well as HTLV-1 proviral load by quantitative PCR analysis. The rationale of this study is that CTLs might attack both ATL cells and HTLV-1-infected T lymphocytes by recognizing the HTLV-1 Tax peptide expressed on the cell surface. This DC vaccine study will demonstrate whether the immunization with HTLV-1 Tax-associated peptide is effective for eliminating ATL.

Expert commentary

Although many chemotherapy regimens have been attempted for aggressive ATL patients based on a similar strategy to that used for aggressive B-cell lymphoma, the outcomes remain poor, probably owing to the innate resistance of ATL cells to multiple cytotoxic agents. This idea is supported by the fact that neither the escalation of dose intensity nor high-dose chemotherapy with the support of autologous SCT was successful. On the other hand, AZT/IFN-α therapy seems to be a promising option, although its efficacy has not yet been confirmed in well-designed prospective studies. Allogeneic SCT has been shown to be effective via a graft-versus-ATL effect through an undetermined immunological mechanism. The induction of the graft-versus-ATL effect and control of the balance in the reaction between graft-versus-ATL and graft-versus-host is probably key to a better outcome. However, several problems still remain unsolved. First, whether chemotherapy or allogeneic SCT is more effective for aggressive ATL has not yet been investigated in comparative clinical studies. Second, whether myeloablative or reduced-intensity conditioning is more appropriate should be determined. Third, finding an appropriate related donor is difficult because siblings are generally as old as the ATL patients, the majority of whom are elderly. As ATL becomes refractory relatively quickly, allogeneic SCT has to be performed as soon as possible after starting chemotherapy (Figure 6). Although cord blood is an alternative and promising source of stem cells, due to it being cryopreserved, stored in cord blood banks and ready for use, the outcome of pilot studies on reduced-intensity transplantation using cord blood is reported to be fairly poor [31]. Another problem is that the experiences and treatment strategies in Western countries and Japan are quite different from each other; the former prefers AZT/IFN-α and the latter prefers intensive chemotherapy with or without allogeneic SCT. Therefore, international collaborative studies should be conducted. In addition, further clinical studies of novel approaches, including new agents such as purine nucleoside phosphorylase inhibitors and HDAC inhibitors, or targeted immunotherapy using anti-CCR4 antibody or DC/peptide vaccine, are warranted.

Five-year view

As ATL is a rare disorder, it is difficult to enroll a sufficient number of patients into clinical studies. Therefore, appropriate patients should be efficiently enrolled into carefully selected well-designed studies. Several clinical studies are currently underway in Japan, including the Phase II study of allogeneic SCT using a myeloablative conditioning regimen by JCOG, and

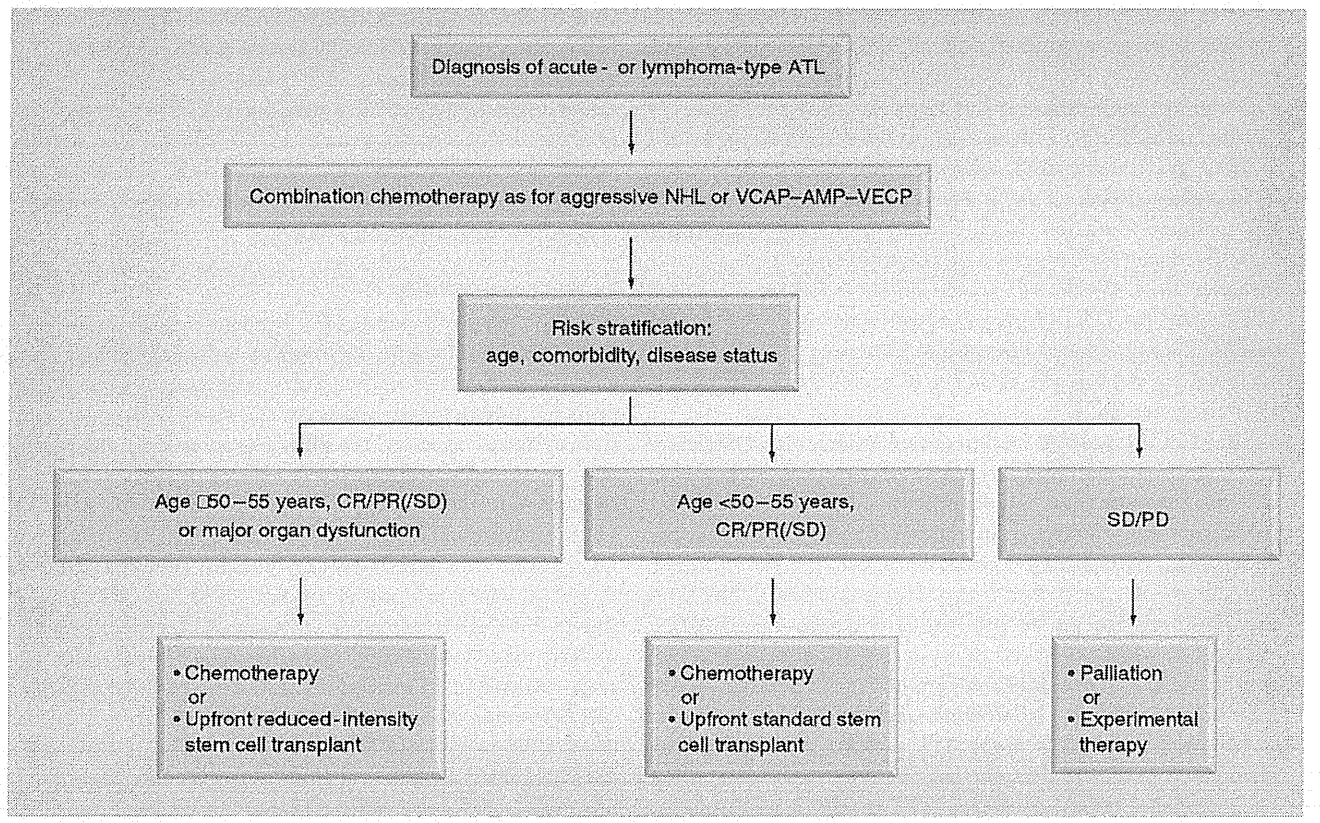

Figure 6. The treatment strategy currently used for aggressive adult T-cell leukemia–lymphoma in Japan. Cord blood transplantation is currently not recommended.
AMP: Doxorubicin, ranimustine and prednisone; ATL: Adult T-cell leukemia-lymphoma; CR: Complete remission; NHL: Non-Hodgkin's lymphoma; PD: Progressive disease; PR: Partial remission; SD: Stable disease; VCAP: Vincrisitine, cyclophosphamide, doxorubicin and prednisone; VECP: Vindesine, etoposide, carboplatin and prednisone.

two multicenter studies of reduced-intensity SCT using unrelated donor bone marrow (Phase I) and related peripheral blood stem cells (Phase II) as stem cell sources. An AZT/IFN-α study is also being prepared in Japan. Recently, a Japanese nationwide prospective study of 1218 asymptomatic HTLV-1 carriers, in which 14 (1.1%) participants progressed to overt ATL after a total follow-up period of 1981.2 person-years, revealed that a higher proviral load in the peripheral blood, advanced age, family history of ATL and first opportunity to identify HTLV-1 infection during treatment for other diseases are independent risk factors for the progression of ATL from carrier status. The study will provide the basis for a strategy to treat high-risk asymptomatic HTLV-1 carriers with, for example, vaccine or AZT/IFN-α to prevent progression to overt ATL [54].

Key issues

- To make decisions for treatment, adult T-cell leukemia–lymphoma (ATL) is first divided into two groups: indolent (i.e., smoldering or chronic type) or aggressive (i.e., acute or lymphoma type).
- The prognosis of indolent ATL is relatively good, whereas that of aggressive ATL is poor, with a median survival of approximately 1 year.
- Only 10–20% of aggressive ATL patients are expected to survive without disease for 2–3 years with intensive chemotherapy.
- Autologous stem cell transplantation (SCT) appears to provide little benefit for ATL patients.
- Approximately a third of aggressive ATL patients are expected to be cured by allogeneic SCT, irrespective of conditioning regimen intensity.
- Allogeneic SCT using myeloablative conditioning is associated with a high mortality rate, whereas reduced-intensity stem cell transplantation is likely to be associated with a high relapse rate.
- Graft-versus-ATL effects and graft-versus-human T-cell lymphotropic virus type I effects are observed after allogeneic SCT.
- Novel approaches, including new agents such as purine nucleoside phosphorylase inhibitors and histone deacetylase inhibitors, or targeted immunotherapy using anti-CCR4 antibody or dendritic cell/peptide vaccines, are warranted.

As the outcome of allogeneic SCT seems to depend on the disease status at transplantation, especially in the case of a reduced-intensity conditioning regimen, the strategy of using new agents is expected for disease control before transplantation. As accumulating evidence is likely to indicate that ATL is potently immunogenic, some clues concerning the target molecule and its related mechanism of action will hopefully be found, so that immunotherapy can be more extensively investigated. Systems of periodic survey of HTLV-1 carriers could also be established to make it possible to identify healthy carriers who are at high risk for progression to overt ATL. Thus, early intervention to prevent the progression of ATL will be more actively investigated.

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