木下朝博	初発限局期DLBCLに対する標準的治療と最新の治療動向	臨床血液	51	1395-1401	2010
伊藤国明	話題、Hodgkin リンパ腫の新たな予後因子	血液腫瘍科	61	719-725	2010
石澤　賢一	B細胞性リンパ腫とB細胞性慢性リンパ性白血病に対するベンダムスチンの有用性	血液・腫瘍科	60	57-64	2010
大間知謙	初発進行期・低リスク群のびまん性大細胞型B細胞性リンパ腫に対する治療.	臨床血液	51	1402-1408	2010
楠本茂、上田龍三	リツキシマブ治療におけるB型肝炎ウイルスの再活性化	血液・腫瘍科	60	36-40	2010

v．研究成果の刊行物・別刷

14 びまん性大細胞型B細胞リンパ腫

木下朝博，満間綾子

疾患の概説

びまん性大細胞型B細胞リンパ腫（diffuse large B-cell lymphoma：DLBCL）は成人非Hodgkinリンパ腫（non-Hodgkin's lymphoma：NHL）の30～40%を占める最も頻度が高い悪性リンパ腫病型で，節性，節外性いずれにも発症する．最も高頻度に発生する節外臓器は消化管であり，皮膚，中枢神経，骨，精巣などさまざまな節外臓器に発生しうる．初発から骨髄，末梢血に病変を伴う場合は少ない．

多くの場合は急速に増大する限局的なリンパ節ないし節外腫瘤として発症するが，ステージングを行えば進行期の場合も多い．中等悪性度NHLの代表的な病型であり，薬物療法や放射線治療などを適切に施行することによって治癒が期待できる疾患である．

治療のための診断・検査

a. リンパ節生検

病理組織検査が診断上最も重要である．リンパ節生検などによって腫瘍組織を生検し，免疫組織染色を含む病理組織検査を行う．合わせてフローサイトメトリーを用いた細胞表面形質解析，染色体分析を行う．

一部のDLBCLには濾胞性リンパ腫に特徴的なt(14;18)(q32;q21)が，また30%では*BCL6*遺伝子が存在する3q27転座が認められる．細胞形質としては一般にS-IgまたはC-Ig$^+$，CD19$^+$，CD20$^+$，CD22$^+$，CD79a$^+$である．一部の症例でCD5やCD10が陽性となり，CD5陽性は予後不良とされる．

b. 臨床病期

Ann Arbor病期分類が用いられる．臨床病期を決定するために，画像診断としては胸部X線，頸部・胸腹部・骨盤部CT，上部消化管検査，2-fluoro-2-deoxy-D-glucose-positron emission tomography（FDG-PET）を行う．2007年に公表された国際ワークショップ判定規準では，DLBCLの治療前病期診断としてFDG-PETを行うことが強く推奨されており，かつ治療効果判定に欠かせない検査と規定されている．

その他に骨髄穿刺・生検が必要である．骨髄浸潤の診断には，骨髄穿刺検体を用いて免疫グロブリン軽鎖を含む細胞表面マーカー解析，および骨髄クロットセクションを用いた病理組織診断を合わせて行う．

c. 予後因子

International Prognostic Index（IPI）は，doxorubicinを含む第一世代以上の併用化学療法で治療されたaggressive lymphomaの予後因子解析に基づいて策定された最も代表的なNHLの予後予測モデルである．IPIで用いられる予後因子は，①年齢（61歳以上），②血清LDH（正常上限を超える），③臨床病期（Ann Arbor ⅢおよびⅣ期），④節外病変数（2ヵ所以上），および⑤performance status（PS）（2以上），の5因子である．5つの予後因子を用いてaggressive lymphomaを4リスクグループに分類する．すなわち該当する予後因子の数が0または1の場合をlow risk，2をlow-intermediate risk，3をhigh-intermediate risk，4または5をhigh riskとする．

また，造血幹細胞移植のような高齢者を対象としない臨床研究への適応を考慮してage-adjusted IPIが策定された．これは，①血清LDH（正常上限を超える），②臨床病期（ⅢおよびⅣ期），および③PS（2以上），の3つの予後因子を用いてIPIと同様に4リスクグループに分類するものである．該当する予後因子の数が0の場合をlow risk，1をlow-intermediate risk，2をhigh-intermediate risk，3をhigh riskとする．

age-adjusted IPI は対象集団の年齢が 60 歳以下に限定されるような若年者だけでなく，61 歳以上に限定されるような高齢者を対象とした臨床試験にも適応可能である．

IPI を限局期症例に適用する場合，臨床病期ⅠおよびⅡ期のみとなるため IPI での臨床病期区分（Ⅰ/Ⅱ vs Ⅲ/Ⅳ）は意味を持たない．同様に節外病変数 2 個以上は臨床病期Ⅳ期となるため無意味である．これらを考慮して，①臨床病期Ⅱ期，②年齢 61 歳以上，③PS 2 以上，④血清 LDH 高値の 4 つの予後不良因子に基づいて層別化する stage-modified IPI が提唱されている．

後述するように，DLBCL に対する標準的治療は rituximab 併用 cyclophosphamide, doxorubicin, vincristine, prednisolone（R-CHOP）療法である．R-CHOP で治療された DLBCL を対象とした研究から提唱された予後予測モデルとして revised IPI がある．これは IPI での予後因子数 0 を very good，1 および 2 を good，3～5 を poor とする予後予測モデルである．very good，good，poor 各群の 4 年無増悪生存率はそれぞれ 94%，80%，53%，4 年生存率はそれぞれ 94%，79%，55% であり予後層別化が可能だった．このように R-IPI は R-CHOP で治療された DLBCL の予後予測モデルとして有用と考えられるが，IPI に置き換わるかどうかについてはさらに検討が必要である．

d. 臓器機能・合併症などの評価

CHOP 療法などのようにアントラサイクリン系薬を含む治療は心毒性を発現する場合があるため，治療前に心エコーを含めた心機能評価を行う．B 型肝炎ウイルス（HBV）キャリア・既感染者では，化学療法施行に伴って HBV 再活性化により肝炎の増悪，劇症肝炎を発症することがあるため，治療前に HBs 抗原，HBs 抗体，HBc 抗体検査を行う．末梢血検査，血液生化学検査によって骨髄機能や肝腎機能など臓器機能の評価を行う．血清 Ca，尿酸にも注意が必要である．

治療の一般方針

DLBCL に対する標準的治療法は rituximab 併用 cyclophosphamide, doxorubicin, vincristine, prednisolone（R-CHOP）療法である．

rituximab は B 細胞表面抗原である CD20 を標的とするマウス・ヒトキメラ型抗 CD20 モノクローナル抗体薬であり，B 細胞リンパ腫に対して高い治療効果を示す．rituximab は主に complement-dependent cytotoxicity（CDC，補体依存性細胞傷害作用）や antibody-dependent cell-mediated cytotoxicity（ADCC，抗体依存性細胞傷害作用）といった機構によって CD20 陽性細胞を傷害する．このほかに免疫反応を介さずアポトーシスを誘導することもその作用機序とされる．rituximab は通常の化学療法薬と薬物有害反応が重複しないために，R-CHOP のように化学療法への追加併用が可能である．

DLBCL に対する R-CHOP の有用性を検証する複数の大規模臨床試験が施行された．代表的な研究としては，GELA が施行した未治療高齢者 DLBCL を対象とした，3 週ごとに行う R-CHOP（R-CHOP-21）と CHOP-21 のランダム化第Ⅲ試験がある．この試験で無イベント生存率（event-free survival：EFS），全生存率（overall survival：OS），完全奏効率（complete response：CR）すべてで R-CHOP-21 が CHOP-21 に優った[1]．その他にも R-CHOP の有用性を示す複数の試験があり，現在では R-CHOP-21 が DLBCL に対する標準的治療とされる．

a. 限局期 DLBCL

限局期には臨床病期Ⅰ期および巨大腫瘤を有しないⅡ期が該当する．1 つの照射野として放射線治療が可能な限局期 DLBCL に対しては，R-CHOP-21 を 3 コースと病変部位への放射線治療（involved-field radiotherapy：IFRT）の併用療法，または R-CHOP-21 を 6～8 コース行う．頭頸部の病変では放射線治療による粘膜障害や唾液分泌障害が問題となるが，このように放射線治療の有害事象が問題となる病変の症例には R-CHOP を 6～8 コース施行する．

stage-modified IPI で 1 つ以上の予後不良因子を有する限局期 DLBCL に対する R-CHOP × 3 + IFRT（rituximab は 4 回投与）の臨床試験における 4 年全生存率は 92%，4 年無増悪生存割合は 88% だった（トピックス①参照）．

b. 進行期 DLBCL

進行期（巨大腫瘤病変を伴う臨床病期Ⅱ期およ

トピックス①

限局期 DLBCL に対する R-CHOP の臨床試験

限局期 DLBCL に対する R-CHOP 療法の大規模試験は乏しく，rituximab 時代における標準治療は未確立と言える．米国において stage-modified IPI で 1 つ以上の risk factor を有する限局期 DLBCL 62 例を対象にして，R-CHOP × 3 + IFRT（rituximab は 4 回投与）の臨床第 II 相試験が施行された[1]．4 年全生存割合は 92%，4 年無増悪生存割合も 88%とその治療成績は良好だった．ただし無増悪生存曲線や生存曲線の平坦化が認められず，再発が持続する問題点が指摘されている．また Miller らによる CHOP × 3 + IFRT の成績[2] と後方視的に比較すると，生存率の改善効果は比較的小さい．

このため，限局期 DLBCL に対する CHOP × 3 + IFRT への rituximab の追加効果は比較的限定的である可能性が指摘されている．

1) Persky DO, et al : Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma : Southwest Oncology Group study 0014. J Clin Oncol 26 : 2258-2263, 2008
2) Miller TP, et al : Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 339 : 21-26, 1998

処方例

R-CHOP-21 療法

リツキサン 1 回 375 mg/m² 点滴静注 day 1
カイトリル 1 回 3 mg/body 点滴静注 day 3
エンドキサン 1 回 750 mg/m² 点滴静注 day 3
アドリアシン 1 回 50 mg/m² 点滴静注 day 3
オンコビン 1 回 1.4 mg/m²（最大 2 mg/day）静注 day 3
プレドニン 100 mg/body 1 日 1 回 朝食後 内服 day 3 ～ 7
以上を 3 週ごとに繰り返す．

リツキサンは抗 CD20 モノクローナル抗体薬であり，腫瘍細胞が CD20 を発現していることを細胞表面マーカー検査や免疫組織学的検査によって確認する．投与にあたっては発熱やアレルギー反応を予防するために，投与 30 分前にカロナール（200 mg）2 T，レスタミン（10 mg）3 T を内服する．リツキサン投与日は CHOP と同日，または CHOP の 1 ～ 2 日前のいずれでもよい．

プレドニンは 65 歳以上では 40 mg/m² に減量する．

び III，IV期）DLBCL に対しては R-CHOP-21 療法を 8 コース施行する．高齢者未治療進行期 DLBCL に対する R-CHOP-21 の治療成績では，5 年全生存率は 58%，5 年無増悪生存割合は 54%だった[2]．

予後不良因子を有する初発進行期 DLBCL に対しては自己造血幹細胞移植併用大量化学療法の有用性を示すデータがいくつか示されているが，現時点では標準的治療として十分に確立したとはいえず臨床試験での検証が必要である．

c. 再発 DLBCL

初回治療による完全寛解後の若年再発性 DLBCL に対しては，救援化学療法が奏効した場合には大量化学療法が第一選択とされる．若年再発例に対する救援化学療法としては cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, rituximab（CHASER）療法などを行い，部分寛解以上の効果が得られた場合には自己造血幹細胞移植併用大量化学療法を行う．高齢者のように移植適応がない場合は rituximab, dexamethasone, etoposide, ifosfamide, carboplatin（R-DeVIC）療法などを行う．なお，年齢や臓器機能に応じて薬剤投与量を調節する．

d. R-CHOP の有害事象とその対策

1）一般的な注意事項

初回 rituximab 投与時には，発熱，悪寒，悪心，頭痛，疼痛，瘙痒，発疹，咳などの輸注関連毒性（infusion reaction）の出現頻度が高いため，入院で治療する．前投薬（解熱鎮痛薬と抗ヒスタミン薬）を行ったうえで投与速度を 25 mL/hr で開始し，1 時間後 100 mL/hr，2 時間後 200 mL/hr まで 1 時間ごとにバイタルサインを確認しながら増量する．第 2 回投与時からは 100 mL/hr から開始し，1 時間後 200 mL/hr とする．

infusion reaction は，血液中に大量の腫瘍細胞がある（25000/μL 以上）患者，脾腫を伴う患者，心機能，肺機能障害を有する患者で発現頻度が高く，血圧下降や気管支痙攣などの重篤な症状を示す場合がある．アナフィラキシー症状，肺障害，心障害（低酸素血症，肺浸潤，急性呼吸促迫症候

群，心筋梗塞，心室細動，心原性ショックなど）での死亡例の報告があるため注意が必要である．

造血器腫瘍の治療では腫瘍細胞が急速に死滅することによって腫瘍崩壊症候群をきたす場合がある．悪性リンパ腫ではリンパ芽球性リンパ腫やBurkitt リンパ腫など高悪性度リンパ腫で起こりやすいとされるが，DLBCL でも腫瘍量が多い場合には注意が必要である．腫瘍崩壊に伴って高尿酸血症，高リン酸血症，低カルシウム血症，代謝性アシドーシス，高カリウム血症をきたし，急性腎不全や呼吸不全が引き起こされる．その予防として，補液で尿量を確保し，重炭酸ナトリウムによって尿のアルカリ化を図り，allopurinol を投与して高尿酸血症を予防するなどの対策を行う．

cyclophosphamide による出血性膀胱炎の予防には点滴などによって尿量を確保する．

vincristine による末梢神経障害（知覚鈍麻，便秘，疼痛など）は用量依存性に生じるため，毎回神経症状の有無について確認し（はしや筆記用具の使用に不自由がないか，ボタンのかけはずしが可能か，手掌のしびれの範囲や進行度など），grade 2 の神経障害では50％に減量し，grade 3 以上では中止する．

2）B 型肝炎キャリア

B 型肝炎ウイルス（HBV）キャリアの患者で rituximab ＋ステロイド併用の全身化学療法施行時には HBV 再活性化により肝炎の増悪，劇症肝炎の報告があるため，投与前に HBs 抗原，HBc 抗体，HBs 抗体のスクリーニングを行う．

HBs 抗原陽性者では肝臓専門医へコンサルトのうえ，抗ウイルス薬（entecavir など核酸アナログ）を投与する．HBs 抗原陰性であっても，HBc 抗体または HBs 抗体陽性例は HBV 再活性化ハイリスクとされ，肝障害・肝炎の出現に先行して HBV-DNA の増加が見られるため，HBV-DNA など肝炎ウイルスマーカーをモニターし，再活性化を認めた場合は抗ウイルス薬を投与する．全身化学療法が終了し免疫抑制から回復した段階での HBV 再活性化のリスクもあり，化学療法終了後12ヵ月までモニタリング継続が望ましい．

3）感染・発熱予防

CHOP では day10 ～ 15 が白血球減少，好中球減少が強く現れる時期である．感染予防，発熱時の対処法を初回入院中に患者に説明しておく．好中球減少時の発熱（febrile neutropenia：FN）には G-CSF 投与を行うが，ASCO ガイドラインに示されたように，65 歳以上の高齢者，全身状態（performance status：PS）不良，FN 発症歴あり，低栄養，骨髄浸潤による血球減少や重篤な併存疾患を持つ場合などでは G-CSF を一次予防として投与する．そのほか *Pneumocystis jirovecii* 肺炎予防のため ST 合剤（バクタ）の予防内服を行う．

e．生活指導

R-CHOP は外来化学療法として行われることが多いため，感染予防法（手洗い，うがい，人ごみでのマスク着用など）について指導する．また発熱時にただちに抗菌薬（クラビット）の内服が開始できるようにあらかじめ処方・指導するとともに，症状が軽微でなければ速やかに病院を受診するように指導する．

トピックス②

R-CHOP の dose intensification（R-CHOP-14）

ドイツでは未治療高齢者 DLBCL を対象として rituximab 併用して 2 週ごとに行う CHOP-14（R-CHOP-14）と rituximab を併用しない CHOP-14 の比較試験（RICOVER-60）が行われた[1]．CHOP-14 が 6 または 8 コース，および rituximab 併用ありまたはなしの合計 4 群のランダム化比較試験である．この試験では高齢者 DLBCL に対しては 6 コースの R-CHOP-14 が標準的治療であるとされた．

ただし，現在 2 週ごとに行う R-CHOP-14 と 3 週ごとに行う R-CHOP-21 の比較試験が複数進行中であり，R-CHOP-14 が標準的治療となるかどうかはこれらの結果を待つ必要がある．

1) Pfreundschuh M, et al：Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas：a randomised controlled trial (RICOVER-60). Lancet Oncol 9：105-116, 2008

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Leukemia & Lymphoma, May 2010; 51(5): 813–821

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ORIGINAL ARTICLE: CLINICAL

Pretreatment total serum protein is a significant prognostic factor for the outcome of patients with peripheral T/natural killer-cell lymphomas

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(Received 14 October 2009; revised 15 February 2010; accepted 20 February 2010)

Abstract

Peripheral T- and NK-cell lymphomas (PT/NKCLs) are relatively rare, and few studies have validated the International Prognostic Index (IPI) for PT/NKCLs in prospective clinical trials. Histopathological specimens from 136 patients, enrolled in six prospective multicenter trials of doxorubicin-containing regimens, with PT/NKCLs were reviewed by six hematopathologists following the WHO classification. This combined analysis demonstrated that the IPI was not predictive of prognosis for patients with PT/NKCLs as previously shown by GELA. In a univariate analysis, low total serum protein (TP) and albumin levels, gastrointestinal tract involvement, and histologic subtype (extranodal NK/T-cell lymphoma, nasal type, and peripheral T-cell lymphoma, unspecified) were significantly associated with reduced survival. In a multivariate analysis, TP ($p = 0.004$) and histologic subtype ($p = 0.024$) remained significant. We discuss the need to establish the importance and meaning of TP and to develop new strategies for patients with PT/NKCLs allowing for TP, especially with worse histologic subtypes.

Keywords: *International Prognostic Index, peripheral T-cell lymphoma, total protein, WHO classification*

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This study was presented in part at the 'Focus on ... ' session, 'T-cell' in the 10th International Conference on Malignant Lymphoma, Lugano, 2008.

ISSN 1042-8194 print/ISSN 1029-2403 online © 2010 Informa Healthcare USA, Inc.
DOI: 10.3109/10428191003721359

Introduction

Peripheral T-cell lymphomas (PTCLs) are relatively rare neoplasms and not equally distributed geographically throughout the world. For instance, PTCLs account for 10% of all non-Hodgkin lymphomas in Western countries [1], but 23% in Japan [2]. Advances in immunophenotyping and molecular genetics have defined several distinct entities of PTCLs that were not identified by the Working Formulation (WF) classification [3]. The third edition of the World Health Organization (WHO) classification system [4] specifies 16 major subtypes of T- and natural killer (NK)-cell lymphomas with characteristic morphologic and immunophenotypic features and clinical manifestations. Although this classification allows different subgroups of patients with T-cell lymphoma to be identified, it does not inform on patient outcome.

The International Prognostic Index (IPI) [5], which was originally constructed for all aggressive lymphomas and is the most widely used index worldwide, has also been reported to predict the prognosis of patients with PTCLs [6–8]. However, the IPI has not been validated for patients with PTCLs who are enrolled in multicenter prospective clinical trials incorporating central pathology review by several pathologists using the WHO classification [4]. Among adult aggressive lymphomas, the T-cell phenotype is associated with a poor prognosis [9–12], except for anaplastic large cell lymphoma (ALCL) [1,8,12]. However, only a few studies have examined prognostic factors or models for PTCLs. A study conducted by the Intergruppo Italiano Linfomi demonstrated that the Prognosis Index for peripheral T-cell lymphoma, unspecified (PTCL-U) (PIT) can be used to predict the survival of PTCL-U [13].

A retrospective analysis of the prognosis of peripheral T- and NK-cell lymphomas (PT/NKCLs) based on retrospective clinical reviews is somewhat cumbersome, primarily due to the heterogeneity of treatment regimens. For this reason, we undertook a combined analysis of multicenter prospective trials conducted by the Japan Clinical Oncology Group – Lymphoma Study Group (JCOG–LSG) during the 1990s with the main endpoint of developing a practical and reproducible method to predict the precise prognosis for patients with PT/NKCLs, as did the Groupe d'Etude des Lymphomes de l'Adulte (GELA), in which patients were treated following the LNH87 or LNH93 protocol [14].

Materials and methods

Patient selection

This study, JCOG0108A, analyzed 1141 patients enrolled in the following six JCOG–LSG multicenter clinical trials for advanced adult aggressive lymphomas according to the WF classification [3] in those days, which were conducted consecutively in the 1990s: JCOG9002, 9203, 9505, 9506, 9508, and 9809. Patients with mycosis fungoides, Sézary syndrome, adult T-cell leukemia/lymphoma (ATLL), and precursor T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) were excluded from all of the studies. Detailed descriptions of the patient eligibility criteria for these six trials were previously described [15–19]. All of the protocols described above, including the informed consent document, were approved by both the JCOG Protocol Review Committee and the institutional review board of each institution. The first edition of JCOG0108A was written on 27 June 2001 and approved by the JCOG Protocol Review Committee on 31 October 2001.

Treatment

All patients were enrolled in multicenter prospective studies and treated with doxorubicin (DXR)-containing second- or third-generation multidrug combination chemotherapies [15,16], or cyclophosphamide (CPA), DXR, vincristine (VCR), and prednisolone (PSL) (CHOP)-like regimens [17–19]. JCOG9002, 9203, and 9809 were clinical trials for patients with all IPI [15,16,19], while JCOG9505 and 9506 were those for high-intermediate/high-risk [17,18], and JCOG9508 was a trial for low-intermediate/low-risk of IPI [18].

Histopathological and immunohistochemical analyses by central review

An expert panel of six hematopathologists (Kiyoshi Mukai, Shigeo Nakamura, Koichi Ohshima, Masahiro Kikuchi, Yoshihiro Matsuno, and Tadashi Yoshino) and two clinicians (Tomomitsu Hotta and Masanori Shimoyama) reviewed the histopathologic diagnosis for 1023 of the 1141 patients enrolled in the six studies. The panel was provided with essential clinical data, including the age and gender of each patient, biopsy site, anatomic disease distribution, and anti-human T-cell leukemia virus type 1 antibody status. A consensus diagnosis was reached following histological review of each biopsy specimen in accordance with the third edition of the WHO classification system [4], including 136 patients diagnosed with PT/NKCLs. Immunohistochemistry using formalin-fixed paraffin-embedded sections and a panel of antibodies (see 'Appendix. Supporting Information') was used. T/NK-cell lineage was assigned only when the neoplastic lymphoid cells expressed at least one of the T/NK-cell antigens, such as CD3, CD45RO,

or CD56, and did not stain for the examined B-cell antigens (CD20 or CD79a).

ALCL was diagnosed for cases with a typical anaplastic morphology or sinus involvement, and a non-T/non-B or a T-cell phenotype, which was identified only by immunohistochemistry, and strong, uniform CD30 expression. For pathological diagnosis of extranodal NK/T-cell lymphoma, nasal type (NKTCL), patient samples were examined by Epstein–Barr virus-encoded small RNA-1 *in situ* hybridization (EBER-ISH). Southern blotting for the T-cell receptor gene rearrangement was not performed.

Prognostic factors

Eighteen clinical, biochemical, and radiologic parameters were analyzed to evaluate their capacity to predict patient outcome. These prognostic factors and risk groups, as defined by the IPI [5], were subjected to univariate analysis. Then, significant variables were included in a Cox multivariate analysis.

Except for the following incomplete data sets, complete data sets were available for all 136 patients with PT/NKCLs, which were diagnosed by central pathological review using data on all prognostic variables as well as overall survival (OS): seven patients did not have accurate pretreatment serum lactate dehydrogenase (LDH) levels, mainly because of a lack of information on the upper limit of the normal range for each institution at that time; one patient was not accurately staged and evaluable for performance status (PS); three patients were not evaluable precisely for the presence of B symptoms; and five, six, four, and four patients did not have pretreatment total serum protein (TP), albumin (Alb), and aspartate transaminase (AST) levels, and hemoglobin (Hb) levels determined, respectively.

Statistical analysis

Multiple statistical analyses were performed by a statistician (Kenichi Yoshimura) in the JCOG Data Center. Comparisons between patient groups were analyzed using a χ^2 test for categorical variables. The OS was calculated using the date of enrollment in each study until the date of death or last follow-up for living patients, and OS curves were estimated using the Kaplan–Meier method. The log-rank test was used to assess the significance of unadjusted differences in OS for each prognostic factor. Prognostic factors with $p < 0.3$ by univariate analysis were included in a multivariate analysis. The multivariate analysis was performed by the Cox proportional hazards model to identify subsets of independent prognostic factors for OS. Two-sided t tests were used to calculate all p-values and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS, version 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

Major clinical characteristics and prognosis of PT/NKCLs compared to diffuse large B-cell lymphoma

The major clinical and biologic characteristics of PT/NKCLs and diffuse large B-cell lymphoma (DLBCL) are summarized in Table I. The statistically significant characteristics for PT/NKCLs were advanced stage, two or more extranodal sites, poorer PS, and presence of B symptoms. When 127 patients with PT/NKCLs with complete data sets available for the IPI were grouped by risk factors, PT/NKCLs showed a higher grade than those with DLBCL (Table I).

The 5-year OS of patients with PT/NKCLs was 46% (95% confidence interval [CI], 38–54%), which was significantly inferior to the 58% 5-year OS (95% CI, 54–62%) of patients with DLBCL. The IPI separated the patients with DLBCL into four risk groups with distinct survival outcomes (data not shown). On the other hand, the OS of patients with PT/NKCLs in the high-risk group was not less than that of patients in either the high-intermediate- or low-intermediate-risk groups (Figure 1), indicating that the IPI model does not fit well for patients with PT/NKCLs.

Table I. Comparison of clinical and biologic characteristics between patients with diffuse large B-cell lymphoma and peripheral T- and NK-cell lymphomas.

Parameter	DLBCL ($n = 642$) (%)	T- and NK-cell lymphomas ($n = 136$) (%)	p-Value
Sex (male/female)	60/40	67/33	0.13
Age ($\leq 60 / > 60$)	59/41	70/30	0.02
Ann Arbor stage (I + II/III + IV)	38/62	19/81	< 0.001
Extranodal sites ($\leq 1 / \geq 2$)	79/21	70/30	0.03
ECOG PS ($0 + 1 / \geq 2$)	84/16	70/30	< 0.001
LDH ($\leq N / > N$)	47/53	41/59	0.24
B symptoms (no/yes)	75/25	47/53	< 0.001
IPI (L/LI/HI/H)	38/31/20/11	27/33/22/18	0.04

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; N, normal; IPI, International Prognostic Index; L, low risk; LI, low-intermediate risk; HI, high-intermediate risk; H, high risk.

Histologic subtypes and OS according to PT/NKCL subtypes

There were 53 patients with PTCL-U, 46 with angioimmunoblastic T-cell lymphoma (AITL), 18 with ALCL, 17 with NKTCL, one with subcutaneous panniculitis-like T-cell lymphoma (SCPTCL), and one with enteropathy-type T-cell lymphoma (ETCL).

A Kaplan–Meier analysis showed that patients diagnosed with PTCL-U and NKTCL had significantly inferior survival curves than patients with ALCL and AITL (Figure 2). The 5-year OS of patients with ALCL, AITL, NKTCL, and PTCL-U was 61% (95% CI, 35–79%), 55% (95% CI, 39–68%), 41% (95% CI, 19–63%), and 38% (95% CI, 25–51%), respectively.

Prognostic parameters for OS in patients with PT/NKCLs

The clinical characteristics of the 136 patients with PT/NKCLs examined using a univariate analysis and their cut-off values are listed in Table II. The following clinical parameters were significantly associated with reduced survival in a univariate analysis: pretreatment serum TP levels, gastrointestinal (GI) tract involvement, histologic subtype, and pretreatment serum Alb levels (Table III). None of the parameters used in the IPI were prognostically significant.

Eight variables reached the cut-off value of $p < 0.3$ in a univariate analysis (Table III) and were subsequently evaluated in a multivariate analysis. Consequently, only pretreatment TP levels (hazard ratio [HR], 2.21; 95% CI, 1.28–3.83; $p = 0.004$) and the histologic subtype (HR, 1.73; 95% CI, 1.08–2.77; $p = 0.024$) remained significant. Pretreatment serum TP levels, with a cut-off value of 6.3 g/dL, which was determined by the lower limit value of the normal range, clearly separated patients with PT/NKCLs into two groups with different outcomes (Figure 3).

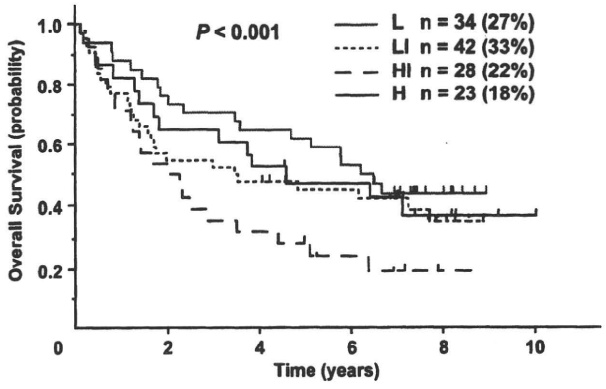

Figure 1. OS according to the IPI. Patients with T- and NK-cell lymphomas ($n = 127$) with complete data sets available for the IPI. L, low risk; LI, low-intermediate risk; HI, high-intermediate risk; H, high risk.

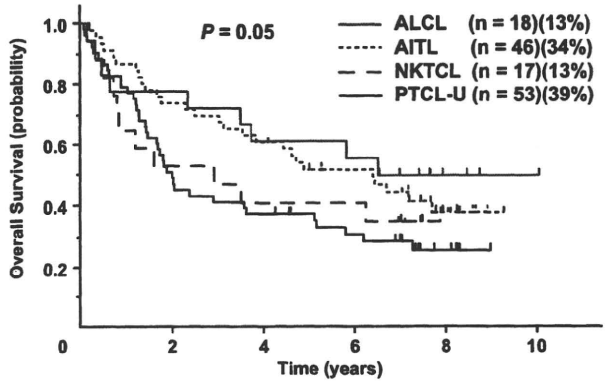

Figure 2. OS according to WHO histologic subtype ($n = 134$). ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; NKTCL, extranodal NK/T-cell lymphoma, nasal type; PTCL-U, peripheral T-cell lymphoma, unspecified.

Comparison of clinical and biologic characteristics among histologic subtypes

The distribution of Ann Arbor stage, PS, LDH, and IPI was unbalanced among histologic subtypes (Table IV). However, the ratio of low serum TP level, which remained significant by the multivariate analysis, was not statistically different among the histologic subtypes, in addition to two or more extranodal sites, BM, and GI tract involvement (Table IV). Patients with NKTCL more frequently had a localized disease and an ambulatory PS (ECOG PS of 0 or 1 was 100%), and less frequently had B symptoms compared with other histologic subtypes. Patients with ALCL, AITL, and PTCL-U had a more advanced disease and lower PS (26–39%), and more than half of them had B symptoms. Seventy percent or more of the ALCL and NKTCL patients were classified as the low/low-intermediate-risk group according to the IPI scoring, while 58% of the AITL patients were in the high-intermediate (HI)/high (H)-risk group, and the proportion of the HI/H-risk group of the patients with PTCL-U was intermediate between that of the HI/H-risk group of patients with ALCL/NKTCL and AITL (Table IV).

Discussion

Both serum TP and Alb levels were prognostic factors in a univariate analysis, but only TP remained significant in a multivariate analysis. Among the prognostic studies to date, only one report found that TP was significant in a multivariate analysis in PT/NKCLs [20]. TP and Alb levels may reflect patient exhaustion resulting from severe constitutional symptoms, or the patient's inability to tolerate

Table II. Clinical and biologic characteristics of 136 patients with peripheral T- and NK-cell lymphomas.

Characteristic and cut-off value	No. of patients with available data	No. of patients	%
Sex	136		
Male		91	67
Female		45	33
Age (years)	136		
≤60		95	70
≥60		41	30
Ann Arbor CS	135		
I, II		26	19
III, IV		109	81
Dimensions of largest tumor	131		
<5 cm		88	67
≥5 cm, <10 cm		29	22
≥10 cm		14	11
Extranodal sites	132		
0, 1		93	70
≥2		39	30
BM involvement	135		
No		106	79
Yes		29	21
GI tract involvement	135		
No		118	87
Yes		17	13
Liver involvement	135		
No		115	85
Yes		20	15
Spleen involvement	135		
No		107	79
Yes		28	21
Other involvement	135		
No		77	57
Yes		58	43
ECOG PS	135		
0, 1		95	70
≥2		40	30
B symptoms	133		
Absent		62	47
Present		71	53
LDH	129		
Normal range		53	41
Higher than normal		76	59
TP (g/dL)	131		
≥6.3		101	77
<6.3*		30	23
Alb (g/dL)	130		
≥3.7		62	48
<3.7*		68	52
AST (IU/L)	132		
≤40		112	85
>40		20	15
Hb (g/dL)	132		
≥10.0		114	86
<10.0		18	14
Histologic subtype	136		
AITL		46	34
ALCL		18	13
SCPTCL		1	1
NKTCL		17	13
PTCL-U		53	39
ETCL		1	1

*The lower limit value of the normal range.
CS, clinical stage; BM, bone marrow; GI, gastrointestinal; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; TP, total protein; Alb, albumin; AST, aspartate transaminase; Hb, hemoglobin; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; SCPTCL, subcutaneous panniculitis-like T-cell lymphoma; NKTCL, extranodal NK/T-cell lymphoma, nasal type; PTCL-U, peripheral T-cell lymphoma, unspecified; ETCL, enteropathy-type T-cell lymphoma.

Table III. Clinicopathological parameters influencing survival of patients with peripheral T- and NK-cell lymphomas in a univariate analysis.

Parameter	Cut-off value	Hazard ratio	*p*-Value
TP* (g/dL)	<6.3†	2.39	0.0003
GI tract involvement*	Yes	1.81	0.049
Histologic subtype*	NKTCL+PTCL-U+ETCL	1.71	0.015
Alb* (g/dL)	<3.7†	1.68	0.021
Extranodal sites*	>1 site	1.46	0.11
Hemoglobin* (g/dL)	<10.0	1.39	0.28
B symptoms*	Present	1.35	0.17
ECOG PS*	>1	1.31	0.24
Ann Arbor stage	>2	1.26	0.42
Age	>60	1.22	0.38
LDH	>1×normal	1.22	0.37
BM involvement	Yes	1.01	0.98

*These variables were used in a multivariate analysis.
†The lower limit value of the normal range.
TP, total protein; GI, gastrointestinal; NKTCL+PTCL-U+ETCL, extranodal NK/T-cell lymphoma, nasal type, peripheral T-cell lymphoma, unspecified, and enteropathy-type T-cell lymphoma versus angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma; Alb, albumin; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; BM, bone marrow.

intensive chemotherapy. One of the potential reasons why TP is superior to Alb as a prognostic factor is that hypergammaglobulinemia might be a relevant and favorable prognostic factor. Unfortunately, in older trials, such as JCOG9002 and JCOG9203, where half of patients with AITL were registered, immunoglobulin levels were not monitored. Patients with TP < 6.3 g/dL were found in 33, 17, 12, and

25% of ALCL, AITL, NKTCL, and PTCL-U, respectively (Table IV). The meaning of TP should be confirmed for each histologic subtype in future studies.

One reason for the conflicting results concerning the histologic subtypes of PT/NKCLs between the studies may be because disease prognosis differs depending on the geographic distribution of the various subtypes [22]. Another considerable reason for the discrepant outcome between the histologic subtypes is that one-third of patients with AITL progress so rapidly that those with a poor performance status (PS) are excluded from prospective multicenter clinical trials. Patients with a PS of 3 were excluded in two of the clinical trials, JCOG9203 and JCOG9809, in the present study.

A recent report from GELA showed that neither the IPI nor the PIT model predicted the survival of patients with AITL [14]. The 5-year OS of patients with AITL in our study population was superior to that described in the GELA study (55% [95% CI, 39–68%) vs. 33% [95% CI, 26–41%] [14]). One possible explanation for this difference is that these studies used different treatments. Another explanation is that the agreement level of the expert hematopathologists with the consensus diagnosis for some of the T-cell lymphoma subtypes was generally poor [21,22], and different AITL diagnostic criteria might have been used for the different study groups.

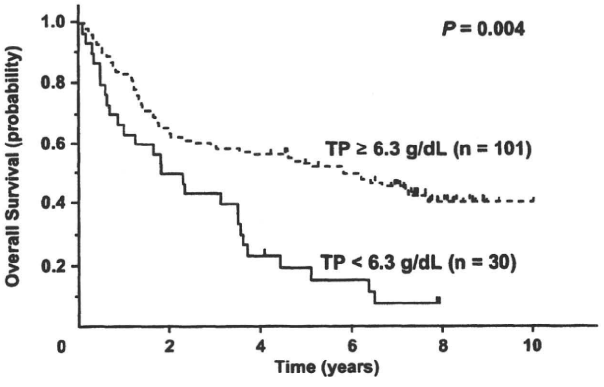

Figure 3. OS according to pretreatment total serum protein levels ($n=131$).

The majority of ALCL cases are positive for the anaplastic large cell lymphoma kinase (ALK) protein, but cases without ALK expression were also included in this category. Unfortunately, the proportion of ALK-negative cases, which usually have a poor prognosis [23], could not be determined in this study. The immunoreactivity to ALK was not systematically assessed, because this distinction was not included in the eligibility criteria in any of the original clinical trials in this study.

The important prognostic factors, as well as prognostic models, may differ according to the treatment regimen. PT/NKCLs are relatively rare, and are treated with various therapies according to the disease state. A Taiwanese group revealed that patients with PTCL who received only CPA, VCR, and PSL as induction chemotherapy had a markedly unfavorable outcome [24]. Therefore, a homogeneous population of patients who have received at least anthracycline-containing regimens should be analyzed when the prognostic factors of PTCL are investigated. Our study was a combined analysis of multicenter prospective clinical trials, as GELA was previously [14]. The IPI was originally described for patients with aggressive lymphomas treated with DXR-containing combination chemotherapies, and has been known to predict the survival of patients with aggressive B-cell lymphomas, as shown in this study and other studies, but not always for patients with PT/NKCLs [21,25]. Moreover, previous reports have shown that the IPI poorly predicts the survival of patients with AITL [14], ALCL [26], PTCL-U [26], or NKTCL [27].

Table IV. Comparison of clinical and biologic characteristics of patients with peripheral T- and NK-cell lymphomas according to histologic subtype.

Parameter	ALCL ($n=18$) (%)	AITL ($n=46$) (%)	NKTCL ($n=17$) (%)	PTCL-U ($n=53$) (%)	p-Value
Sex (male/female)	72/28	65/35	82/18	62/38	0.45
Age (≤60/>60)	72/28	65/35	65/35	74/26	0.79
Ann Arbor stage (I+II/III+IV)	33/67	2/96	47/53	21/79	<0.001
Extranodal sites (≤1/≥2)	83/17	67/26	65/35	66/32	0.57
ECOG PS (0+1/≥2)	61/39	59/39	100/0	74/26	0.01
LDH (≤N/>N)	67/28	15/83	71/18	38/57	<0.001
B symptoms (no/yes)	44/56	35/63	71/29	45/51	0.10
IPI (L/LI/HI/H)	50/22/11/11	7/33/30/28	41/29/18/0	28/34/17/15	0.003
BM involvement (no/yes)	100/0	67/30	88/12	75/25	0.12
GI tract involvement (no/yes)	83/17	96/2	100/0	77/23	0.54
TP <6.3 (no/yes)	61/33	80/17	82/12	72/25	0.62

ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; NKTCL, extranodal NK/T-cell lymphoma, nasal type; PTCL-U, peripheral T-cell lymphoma, unspecified.

There are several potential reasons why the IPI model did not retain its prognostic significance for patients with PT/NKCLs in our study. The extent of disease and presence of extranodal sites were no longer significant prognostic factors, probably because PT/NKCLs *per se* are characterized by both the presentation of disease in an advanced stage, III or IV [10,12,13], and in two or more extranodal sites (Table I) [12,13]. Moreover, DLBCL has different characteristics from PT/NKCLs, which are more frequently associated with a poor PS and B symptoms [10,12] (Table I). The IPI incorporates age, LDH, and the abovementioned factors, except for B symptoms. Consequently, PT/NKCLs should have different prognostic factors than those for DLBCL.

An early GELA study noted that the freedom-from-relapse survival of patients with PTCL, unlike patients with B-cell lymphoma, was not impacted by either LDH or bone marrow (BM) involvement [10]. BM involvement, which is one of the risk factors adopted in the PIT, was not a significant adverse factor in our study including other histologic subtypes besides PTCL-U. Although patients with NKTCL had the property of a localized disease, 53% of them had advanced diseases, and 12% of them had BM involvement in this study (Table IV). Instead of BM involvement, we found that GI involvement was significantly associated with survival in a univariate analysis. However, when we tried additional univariate analysis excluding NKTCL and ETCL, this was not significant, although the GI tract was not involved in any patients with NKTCL, as shown in Table IV, and there was a sole patient with ETCL.

New prognostic models have been proposed for certain categories of PT/NKCLs, such as the PIT model [13] and clinical–pathologic prognostic score [28] for PTCL-U and a prognostic model for NKTCL [29]. In addition, new molecular prognostic markers such as CD15 [28], EBER-ISH [25,30], cytotoxic T-cell phenotype [31,32], various chemokine receptors [33,34], Ki-67 [28], and the proliferation-core signature [35] have been investigated for PTCL-U. As for NKTCL, P19 [27], Ki-67 [36], and FOXP3-positive regulatory T-cells [37] have been proposed as predictors for clinical outcome. Although biochemical data, β_2-microglobulin combined with the adjusted IPI, has been reported to predict the outcome after autologous hematopoietic stem cell transplant in relapsed/refractory PTCL [38], we had no available data to analyze in four out of the six clinical trials included in this study. Allowing for or to validate these prognostic factors with homogeneous treatment, histology-specific therapy is warranted. As PT/NKCLs have variable characteristics dependent on histologic subtype (Table IV), patients with PT/NKCLs should not be studied as a whole, and studies in future should be performed for each histologic subtype. However, pretreatment serum low TP levels might be an adverse prognostic factor independent of histologic subtype, because its frequency was not different among the histologic subtypes (Table IV). Therefore, this prognostic factor should be noteworthy even with regard to each histologic subtype.

In conclusion, TP is a significant prognostic factor to predict the outcome of PT/NKCLs. A validation study is required in order to establish the importance and meaning of TP in patients with each histologic subtype of PT/NKCLs. Further, the new therapeutic strategies, including new agents and/or first-line high-dose chemotherapy followed by autologous or allogeneic hematopoietic stem cell transplant, should be explored for patients with lower TP levels and/or higher-risk histologic subtypes in the future.

Acknowledgements

We thank Masahiro Kikuchi (Fukuoka University), Yoshihiro Matsuno (Hokkaido University), and Tadashi Yoshino (Okayama University) for conducting the pathology review and serving as members of an expert panel, and Yoshihiro Matsuno for his assistance in writing the histopathological and immunohistochemical by central review analyses portion of the manuscript.

Declaration of interest: This study was supported by Grants-in-Aid No. 2S-1, 5S-1, 8S-1, 11S-1, 11S-4, 14S-1, 14S-4, 17S-1, and 17S-5 for Cancer Research from the Ministry of Health, Labor and Welfare of Japan.

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Appendix. Supporting information

Antibodies used for immunophenotyping.

Antigen	Antibody	Poly/Mono	Source	
CD20	L26	M	DAKO	Glostrup, Denmark
CD3	PS1	M	Novocastra	Newcastle, UK
CD4	1F6	M	Novocastra	Newcastle, UK
CD5	4C7	M	Novocastra	Newcastle, UK
CD8	4B11	M	Novocastra	Newcastle, UK
CD10	56C6	M	Novocastra	Newcastle, UK
CD15	MMA	M	Becton Dickinson	San Jose, CA, USA
CD21	1F8	M	DAKO	Glostrup, Denmark
CD23	1B12	M	Novocastra	Newcastle, UK
CD30	BerH2	M	DAKO	Glostrup, Denmark
CD45	LCA	M	DAKO	Glostrup, Denmark
CD45RO	UCHL1	M	DAKO	Glostrup, Denmark
CD56	NCC-LU-243	M	Nihon Kayaku	Tokyo, Japan
CD79a	CD79a	M	DAKO	Glostrup, Denmark
CD246	ALK1	M	DAKO	Glostrup, Denmark
bcl-2	124	M	DAKO	Glostrup, Denmark
cyclin D1	SP4	M	Nichirei	Tokyo, Japan
MUM1	MUM1P	M	DAKO	Glostrup, Denmark
Ki-67	MIB1	M	DAKO	Glostrup, Denmark
TdT	anti-TdT	P	DAKO	Glostrup, Denmark

TdT, terminal deoxyribonucleotide transferase; M, monoclonal; P, polyclonal.

Int J Hematol (2010) 91:446–455
DOI 10.1007/s12185-010-0533-9

ORIGINAL ARTICLE

Prognostic analysis and a new risk model for Hodgkin lymphoma in Japan

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Received: 6 July 2009 / Revised: 5 February 2010 / Accepted: 8 February 2010 / Published online: 3 March 2010

Abstract The Japan Clinical Oncology Group conducted two multicenter phase II trials in 200 patients with advanced Hodgkin lymphoma (HL) in the 1990s. Among 181 patients whose histopathological specimens were available and reviewed by 6 hematopathologists, 167 (92.3%) were diagnosed with HL. Five-year overall survival (OS) among these 167 patients was 88.3%, including 89.2% among nodular sclerosis and 82.2% among mixed cellularity cases. International prognostic score was not closely associated with OS. Seven unfavorable prognostic factors for OS on univariate analysis were male, B symptoms, clinical stage of III

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or IV, elevated serum LDH, elevated alkaline phosphatase, elevated β2-microglobulin, and pathological subtype (mixed cellularity and lymphocyte depletion). On multivariate analysis, male [HR 3.30 (95% CI 1.15–9.52, $p = 0.027$)] and elevated serum LDH [HR 2.41 (95% CI 1.07–5.43, $p = 0.034$)] were independent factors for OS. Based on these prognostic factors, the 5-year OS was 95.7% in the low-risk group (no adverse factor), 87.9% in the intermediate-risk group (1 adverse factor) and 73.3% in the high-risk group (2 adverse factors). This simple prognostic model for HL warrants further validation studies.

Keywords International prognostic score · Multicenter phase II trial · Prognostic factor · Overall survival · Male gender · LDH

1 Introduction

Most of the patients with advanced Hodgkin lymphoma (HL) could be induced into complete remission (CR) with state-of-the-art combination chemotherapy or chemo-radiotherapy, and in patients with advanced HL who relapsed after achieving CR, there are some therapeutic options for curing the disease, including conventional salvage chemotherapy and high-dose chemotherapy followed by autologous stem-cell transplantation [1]. However, the excellent outcomes in the initial treatments for HL do not necessarily result in excellent survival, because 20–30% of patients with advanced HL are not cured of their disease, and moreover, the treatments are associated with increased risks of late toxicities such as secondary malignancies, cardiopulmonary toxicities, and cerebrovascular diseases [2–5]. It still seems to be necessary to identify the high-risk group of the minority of patients with fatal outcome.

Many prognostic factors for failure-free survival have been described in patients with advanced HL. These included age, sex, clinical stage, B symptoms, number of nodal sites, laboratory data such as serum albumin, hemoglobin, white cell count, lymphocyte count, etc. [6]. The international prognostic score (IPS) [7] was widely accepted as the prognostic index in advanced HL. However, only 7% of the patients had the worst adverse score of 5 or higher of IPS which represents a very high risk, and was associated with 56% of the overall survival (OS) at 5 years. Thus, it was concluded that a distinct group of patients at very high risk could not be identified by the IPS [7].

Considering the various effective treatment options and their late toxicities, it is important to identify the prognostic factors for OS in patients with advanced HL. In particular, this is relevant to the question of whether early high-dose chemotherapy with autologous stem-cell transplantation should be used as a consolidation therapy in patients with responses to induction therapy, who are nevertheless considered to remain at high risk for relapse. To address the ability to predict the prognosis of patients with advanced HL, we analyzed patients with advanced HL enrolled in the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG–LSG) trials. The aims of this study were to validate the IPS in terms of OS, to evaluate the OS according to several prognostic factors including histological subtypes of HL, and to find a better prognostic model for patients with advanced HL, who were enrolled in JCOG–LSG trials with state-of-the-art combination chemotherapy or chemo-radiotherapy.

2 Patients and methods

2.1 Patients and treatments

The JCOG–LSG conducted two multicenter phase II trials for advanced HL in the 1990s that tested the efficacy of the ABVd regimen (JCOG9305) [8] and ABV regimen followed by involved-field radiotherapy (IF-RT) (JCOG9705) [9]. Major eligibility criteria were age between 15 and 69 years, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 in the two trials, and clinical stage of II, III or IV in JCOG9305 and clinical stage of IB, IIB, III, or IV or any stage with bulky lesion in JCOG9705. Bulky lesion was defined as a mass of at least 10 cm (largest diameter) and a bulky mediastinum (ratio of the mediastinum to the thorax of at least one-third at the level of the largest diameter while the patient was standing). A total of 128 patients from 35 participating institutes were enrolled in JCOG9305 between 1993 and 1997 to assess the efficacy of the ABVd regimen, which consisted of doxorubicin, bleomycin, vinblastine and a reduced dose of dacarbazine of two-thirds (250 mg/m^2) of that in the original ABVD regimen. The reasons for modification of

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the original ABVD regimen in both JCOG studies were that dacarbazine was highly emetic and it was not approved for the treatment of HL in Japan at that time. In JCOG9705, a total of 72 patients from 25 participating institutes were enrolled between 1998 and 2000 to assess the efficacy of the ABV regimen, in which the dose of doxorubicin was increased to 120% of that in the original ABVD regimen and dacarbazine was not utilized. Patients were evaluated for response after 4 cycles of chemotherapy. All patients received 2 additional cycles of chemotherapy. For those with CR after 4 cycles, chemotherapy was finished after a total of 6 cycles. Patients who were in CR or uncertain CR (CRu) after 6 cycles were given 2 additional cycles of chemotherapy. In patients with bulky lesions, IF-RT with 30–40 Gy was added if patients entered into CR or CRu after 4 or 6 cycles. Regardless of whether the lesion was bulky or non-bulky, IF-RT was added if patients entered into partial remission (PR) in JCOG9705.

CR was defined as the disappearance of all measurable or assessable diseases and all signs and symptoms of the disease lasting for at least 4 weeks. PR was defined as a reduction of 50% or greater in the sum of the perpendicular diameters of all measurable lesions and the appearance of no new lesions for at least 4 weeks. CRu was defined as the maintenance of PR for at least 3 months without any treatment. Progressive disease was defined as an increase of 25% in the size of any lesion or development of any new lesions. Relapse was defined as an increase of 25% in the size of any lesion or development of any new lesions in CR or CRu patients. The details of the results of each clinical study will be published elsewhere.

All of the protocols described above including the informed consent document were approved by both the JCOG Protocol Review Committee and the institutional review board of each institution. The protocol of JCOG0108A, an ancillary study with secondary use of the data acquired by the above-mentioned JCOG studies, was also approved by the JCOG Protocol Review Committee.

2.2 Consensus diagnosis

The procedure of reaching a consensus diagnosis of HL according to the WHO classification has been described [10]. Briefly, 6 hematopathologists consisting of 4 panelist pathologists and 2 consulting pathologists reviewed the histopathological specimens independently. Immunohistochemical studies were conducted on paraffin sections by means of the avidin–biotin–peroxidase complex technique and a panel of monoclonal antibodies including antibodies against CD20 (L26; DakoCytomation, Glostrup, Denmark), CD3 (PS-1; Novocastra, Newcastle, UK), CD15 (MMA; Becton Dickinson, San Jose, CA, USA) and CD30 (BerH2; DakoCytomation, Glostrup, Denmark). All 6 hematopathologists and 1 hematologist performed the central pathologic review, in which the case report forms of the patients were available for reference of clinical information. A consensus diagnosis was established when agreement was reached by three-fourths or greater majority of the 4 panelist pathologists with no opposition from the 2 consulting pathologists and the hematologist. The cases with discordant pathological diagnosis were re-evaluated until agreement by two-thirds or greater majority was reached among the 6 pathologists by means of reconciliation. Then, a consensus diagnosis was made. The present study included patients in two multicenter phase II trials for advanced HL who were diagnosed with HL by central pathological review.

2.3 Statistical analysis

All statistical analyses were performed by a statistician (K.Y.) at the JCOG Data Center. Patients with lymphocyte depletion had been reported as having a worse prognosis than those with other subtypes [11], but this subgroup contained only 7 patients in this study. Therefore, patients with lymphocyte depletion were grouped together with patients with mixed cellularity who had also been shown to have a worse prognosis [12]. OS was the endpoint of all statistical analyses. OS was calculated from the date of enrollment in respective study to the date of death from any cause or to the date of last follow-up in living patients. OS was estimated by the Kaplan–Meier method. The log-rank test was used to assess the significance of unadjusted differences in OS for each prognostic factor. Multivariate analysis was performed by the Cox proportional hazards model to identify subsets of prognostic factors for OS. All p values were two-sided and p values less than 0.05 were considered significant. There is no widely agreed approach to building a multivariate prognostic model from a set of candidate predictors [13, 14] and, in consideration of the limitation of events in our study, the data were analyzed from points of significancy and parsimony. A prognostic model was established by fitting all variables that significantly influenced OS in multivariate analysis, and the risk groups were identified according to the established model. For comparing OS between the risk groups, the overfitting-corrected p values were derived by fivefold cross-validation. All statistical analyses were performed using SAS release 9.1.3 (SAS Institute, Inc., Cary, NC).

3 Results

3.1 Histopathological distribution

Among the 200 patients from 41 participating institutes in Japan who were enrolled in two multicenter phase II trials

Table 1 Histopathological distribution of advanced HL among 167 patients

	Number of patients (%)
Nodular lymphocytic predominance	2 (1.2)
Nodular sclerosis	115 (68.9)
Lymphocyte-rich	3 (1.8)
Mixed cellularity	34 (20.4)
Lymphocyte depletion	7 (4.2)
Unclassifiable	6 (3.6)

for advanced HL (128 in JCOG9305 and 72 in JCOG9705), histopathological specimens from 181 patients were available and reviewed, and a consensus diagnosis of HL was reached in 167 (92.3%) (107 in JCOG9305 and 60 in JCOG9705) according to the WHO classification. The remaining 14 patients were diagnosed with diffuse large B cell lymphoma ($n = 4$), T cell-rich B cell lymphoma ($n = 4$), anaplastic large cell lymphoma ($n = 1$), angioimmunoblastic T cell lymphoma ($n = 1$) or other ($n = 4$). The histopathological distribution of the 167 patients with HL is shown in Table 1. Among the HLs, nodular sclerosis ($n = 115$) comprised 68.9% of the whole HL and mixed cellularity ($n = 34$; 20.4%) was the next most frequent subtype in Japan.

3.2 Clinical characteristics

Data from these 167 patients with HL were analyzed. Their clinical characteristics are shown in Table 2. The median age of the patients at diagnosis was 31 years (range 15–69 years). There was a slight male predominance with males comprising 55%. Seventy-six patients (45%) had B symptoms and 49 patients (29%) had extranodal sites.

3.3 OS according to histology and IPS

The 5-year OS of the 167 patients was 88.3% (Fig. 1) (92.3% in JCOG9305 and 81.3% in JCOG9705). The median OS of patients with mixed cellularity was 7.5 years, and those of patients with other histological subtypes was longer than 7.5 years. The 5-year OS of patients with the main histological subtypes was 89.2% in nodular sclerosis and 82.2% in mixed cellularity. The 5-year OS among patients with IPS score of 0, 1, 2, 3, 4, or 5 + 6 was 100% (15 patients), 95.5% (47), 87.5% (40), 86.1% (38), 76.6% (22), or 60.0% (5), respectively (Fig. 2a). Therefore, we failed to identify very high-risk patients by IPS in our study. The OS among patients according to IPS score of 0–2 or 3 and higher is shown in

Table 2 Patient characteristics ($n = 167$)

	Number of patients (%)
Sex	
Male	92 (55.1)
Female	75 (44.9)
Age (years)	
≥45	45 (26.9)
<45	122 (73.1)
Performance status (0/1/2/3)	108/49/7/1
B symptoms	
Yes	76 (45.5)
No	89 (53.3)
Clinical stage	
I/II	83 (49.7)
III	49 (29.3)
IV	35 (21.0)
Bulky mass	
Present	45 (26.9)
Absent	121 (72.5)
Extranodal sites (0/1/≥2)	106/35/14
Sites of organ involvement	
Liver (yes)	11 (6.6)
Lung (yes)	16 (9.6)
Bone marrow (yes)	10 (6.0)
Other (yes)	29 (17.4)
Baseline hematological data	
Hemoglobin (<10.5 g/dl)	28 (16.8)
White blood cells (≥15000/μl)	25 (15.0)
Lymphocytes (<600/μl or <8%)	32 (19.2)
Platelets (<100000/μl)	1 (0.6)
Albumin	
<4 g/dl	99 (59.3)
≥4 g/dl	68 (40.7)
Serum LDH	
Elevated	56 (33.5)
Normal	110 (65.9)
Alkaline phosphatase	
Elevated	74 (44.3)
Normal	92 (55.1)
CRP	
Elevated	128 (76.6)
Normal	29 (17.4)
β2-Microglobulin	
>2 mg/l	39 (23.3)
≤2 mg/l	72 (43.1)

Data on performance status, B symptoms, bulky mass, extranodal sites, serum LDH, alkaline phosphatase, CRP or β2-microglobulin were missing in 2, 2, 1, 12, 1, 1, 10 or 56 patients, respectively

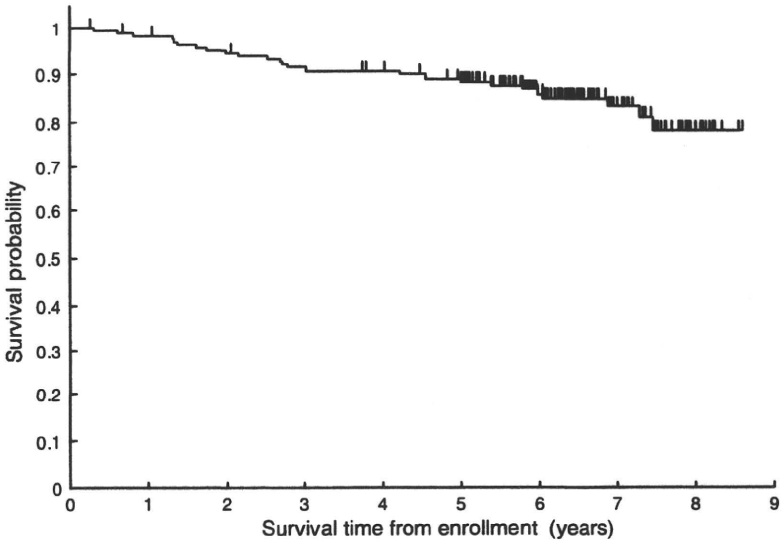

Fig. 1 Kaplan–Meier curves for overall survival among all patients with HL ($n = 167$)

Fig. 2b. An IPS score of 3 or greater was not a significant unfavorable prognostic factor for OS [HR 2.39 (95% CI 1.10–5.21, $p = 0.03$) by univariate analysis and HR 1.20 (95% CI 0.50–2.89, $p = 0.68$) by multivariate analysis with adjustment of other covariates, which were significant in univariate analysis] and thus, IPS was not closely associated with OS. Therefore, we attempted to identify the prognostic factors for OS in Japanese patients with advanced HL by central pathological review.

3.4 Unfavorable prognostic factors by multivariate analysis

Seven unfavorable prognostic factors for OS identified by univariate analysis were male, elevated β2-microglobulin, B symptoms, elevated serum LDH, elevated alkaline phosphatase, clinical stage of III or IV and pathological subtype (mixed cellularity and lymphocyte depletion) (Table 3). Although data of β2-microglobulin were available in only 111 patients (66%), we performed multivariate analysis including β2-microglobulin, but no significant factor was detected. Then, the β2-microglobulin level was excluded from the final multivariate analysis. Male [HR 3.30 (95% CI 1.15–9.52, $p = 0.027$)] and elevated serum LDH [HR 2.41 (95% CI 1.07–5.43, $p = 0.034$)] were significant unfavorable prognostic factors for OS on multivariate analysis (Table 4). Besides, male and elevated serum LDH remained significant in the multivariate analysis including albumin (data not shown). Similarly, elevated serum LDH remained significant in the multivariate analysis including IPS (each 6 categories and 0–2 or 3–6) after sex was excluded (data not shown).

The OS by sex and serum LDH among patients with HL excluding those with unclassifiable histopathology is shown in Fig. 3a and b, respectively. The 5-year OS was 82.4% in males and 94.4% in females, and 82.4% in patients with elevated serum LDH and 90.5% in patients with normal serum LDH.

3.5 Risk group model

The two important prognostic factors identified by the multivariate analysis, i.e., male and elevated serum LDH, were combined in a prognostic index to create risk groups with possible values of 0, 1 and 2 in order of worsening prognosis. Hazard ratios of the final model were as follows: male [HR 4.91 (95% CI 1.84–13.13, $p = 0.002$)] and elevated serum LDH [HR 2.72 (95% CI 1.25–5.89, $p = 0.01$)]. The 5-year OS among patients with HL excluding those with unclassified histopathology was 95.2% in the low-risk group (no adverse factor, $n = 47$), 87.9% in the intermediate-risk group (1 adverse factor, $n = 86$) and 73.3% in the high-risk group (2 adverse factors, $n = 27$). Data on serum LDH were missing in 1 patient. The OS curves of the 3 risk groups are shown in Fig. 4 (corrected $p = 0.004$ by fivefold cross-validation).

4 Discussion

It is recognized that there is an uneven geographical distribution of malignant lymphomas throughout the world. Namely, the incidence of T cell lymphoma is relatively high in Asia compared with Western countries. On the contrary, the incidence of HL in Japan was reported to be 4.4% of malignant lymphomas and this is relatively low compared with those in Western countries [11, 15, 16]. The low incidence of HL in Japan limited the evaluation of the