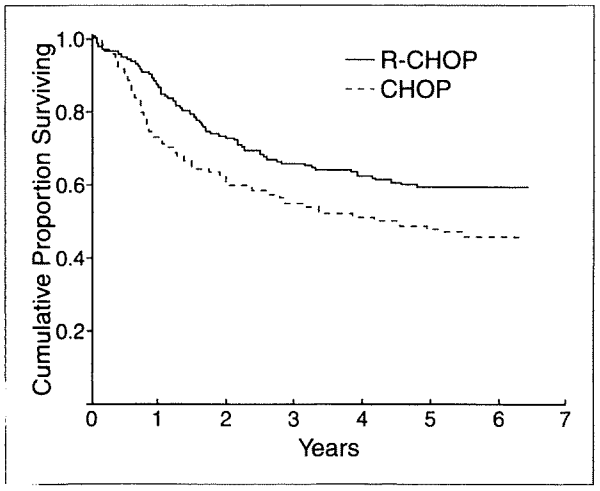

図1 高齢者DLBCLを対象としたR-CHOP療法とCHOP療法のランダム化比較試験での生存期間
（文献[1]より引用改変）

表1 International Prognostic Index（IPI）およびage-adjusted IPI

IPIでの予後因子	予後不良因子
年齢	61歳以上
血清LDH	正常上限を超える
PS	2～4
病期	III または IV
節外病変数	2以上
Age-adjusted IPIでの予後因子	予後不良因子
病期	III または IV
血清LDH	正常上限を超える
PS	2～4

IPI，age-adjusted IPIともに予後因子の数によって4リスクグループに分類する．
IPI；0または1：low risk，2：low-intermediate risk，3：high-intermediate risk，4または5：high risk．
Age-adjusted IPI；0：low risk，1：low-intermediate risk，2：high-intermediate risk，3：high risk

response（PR）が得られた場合にさらにrituximab維持療法を施行する群としない群に割り付ける複雑な試験デザインである[3]．3年failure free survival（FFS）はR-CHOPがCHOPに勝った．また維持療法割り付け後2年でのFFSでは維持療法施行群が維持療法を施行しない群に勝った．ただしOSではR-CHOPとCHOP，および維持療法の有無によって有意差を認めなかった．その理由はCHOP群では維持療法が有効だったのに対しR-CHOP群では有効性が乏しかったためとされた．維持療法を施行しなかった例に限ればR-CHOPはCHOPに対してFFS，OSともに有意に勝っていた．

MInT studyでは予後不良因子が少ない若年者DLBCLを対象として，CHOP-like chemotherapyとrituximabを併用したCHOP-like chemotherapyが比較された[4]．対象は18歳から60歳，臨床病期はbulky diseaseを有するI期，およびII～IV期，age-adjusted IPIでlow riskおよびlow intermediate risk groupに属する予後良好なDLBCLである．Rituximab併用化学療法施行群は化学療法群に対してEFS，OSともに勝っていた．

さらにドイツではrituximab併用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[5]．61歳から80歳の高齢者DLBCLを対象として，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群にランダム割り付けを行って比較検討した．評価可能1,222例の解析で，6コースのCHOP-14と比べた場合3年EFSはR-CHOP-14 6コース，8コースともに有意に優れていた．3年OSについてはR-CHOP-14はR-CHOP-14に有意に勝ったが，R-CHOP-14 8コースについてはCHOP-14 6コースと有意差を認めなかった．この結果から高齢者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．

以上に示したような大規模試験の結果から，R-CHOPは進行期DLBCLに対する標準的治療法として確立したといえよう．

International Prognostic Index（IPI）

International Prognostic Index（IPI）はdoxorubicineを含む第1世代以上の併用化学療法で治療されたaggressive lymphomaの予後因子解析から提唱されたもっとも代表的なNHLの予後予測モデルである[6]．IPIでは5つの予後因子を用いて4リスクグループに分類する．5つの予後因子は，年齢（61歳以上），血清LDH（正常上限を超える），臨床病期（Ann Arbor III およびIV期），節外病変数（2か所以上）およびPerformance status（PS）（2以上）である（表1）．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

表2　R-CHOPで治療されたDLBCLのIPIおよびR-IPIによる予後

リスクグループ	リスク因子数	症例，%	4年PFS，%	4年OS，%
Standard IPI				
Low	0，1	28	85	82
Low-intermediate	2	27	80	81
High-intermediate	3	21	57	49
High	4，5	24	51	59
Revised IPI				
Very good	0	10	94	94
Good	1，2	45	80	79
Poor	3，4，5	45	53	55

IPI：international prognostic index, PFS：progression free survival, OS：overall survival

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も提唱された．これは血清LDH(正常上限を超える)，臨床病期(IIIおよびIV期)およびperformance status(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(表1)．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．

DLBCLに対するRevised IPIの提唱

IPIがR-CHOPで治療されたDLBCLに対しても予後予測モデルとして有用かどうかについてはBritish Columbiaからの報告がある[7]．R-CHOPで治療されたDLBCL 365例について解析したところ，IPIはR-CHOPで治療されたDLBCLに対しても予後予測モデルとして有用だが，lowとlow-intermediate risk，およびhigh-intermediateとhigh riskの予後層別化が不良であり，risk group別でみた場合には2群にしか層別化できなかった．このため，IPIでの5つの予後因子数ごとに解析すると，リスク数が0個，1および2個，3～5個の予後が類似していたため，予後因子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，Revised IPI(R-IPI)が提唱された．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，予後が異なる3群に分類可能だった(表2)．このようにR-IPIはR-CHOPで治療されるDLBCLの予後予測モデルとして有用と考えられるが，IPIを置き換えるかどうかについてはさらに検証が必要と考えられる．

ところで，R-IPIに関する報告には2つの重要なメッセージが含まれている．第1は，DLBCLの予後がR-CHOPによって大きく改善しており，IPIまたはR-IPIいずれのモデルによっても生存率が50%を下回るような予後不良群が同定できなかったという事実である．今後は臨床試験の立案や結果の解釈を行う場合などにおける重要な基礎データになると考えられる．第2は無増悪生存率と生存率がきわめて類似しているという点である．これはR-CHOPで治癒が得られなかった患者では後治療があまり有効ではない可能性を示唆している．R-CHOPで再発・再燃または治療抵抗性のDLBCLに対する後治療についての検討が必要であろう．

DLBCLにおける生物学的予後因子のR-CHOP時代における意義

DLBCLでは，IPIやR-IPIのような臨床的予後因子のみならず，生物学的予後因子がいくつも知られている．これらの中でもっとも重要と思われるものにDNAマイクロアレイを用いた遺伝子発現プロフィール解析から同定されたDLBCL亜型がある[8]．すなわち正常胚中心B細胞を特徴づける遺伝子群の高発現を認めるgerminal center B-cell-like(GCB)DLBCL，活性化B細胞を特徴づける遺伝子群の高発現を認めるactivated B-cell-like DLBCL，およびいずれの遺伝子群についても高発現を認めないtype 3 DLBCLの3亜型である．生存期間は各亜型によって異なり，GCB

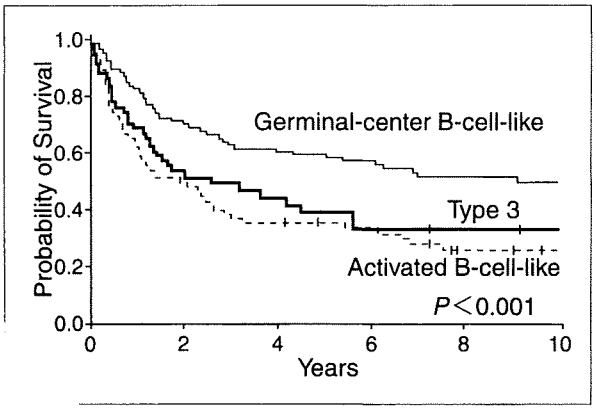

図2 DNAマイクロアレイによる遺伝子発現プロフィール解析で同定されたDLBCL亜型の生存期間
治療にはrituximabは使用されていない．Germinal center B-cell-like DLBCLに比べてactivated B-cell like DLBCLやtype 3 DLBCLの予後が不良だった．
（文献[8]より引用改変）

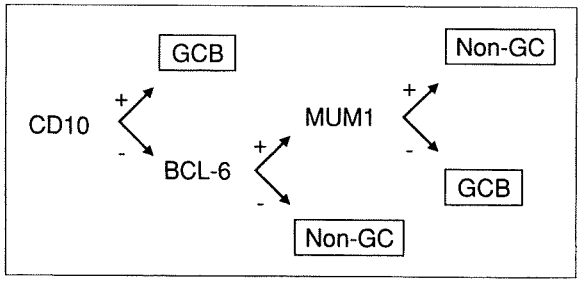

図3 免疫組織学的方法によるDLBCL亜型診断のフローチャート （文献[9]より引用改変）

DLBCLの5年生存率は60%だったのに対して，type 3 DLBCLでは39%，activated B-cell like DLBCLでは35%と有意に予後不良だった(図2)．

DNAマイクロアレイは臨床現場で広く一般的に応用可能な技術ではないため，免疫組織学的検索により上記DLBCL亜型を同定する方法が報告されている．HansらはCD10, BCL-6, MUM-1の発現について免疫組織学的に検討することによってDLBCL亜型の同定が可能であり，GCB DLBCLとnon-GCB DLBCLに分類するとnon-GCB DLBCLの予後が不良であることを報告した(図3)[9]．

このように遺伝子発現プロフィールから同定されたDLBCL亜型の提唱はDLBCL研究にきわめて大きなインパクトを与えた．このDLBCL亜型は免疫組織学的な検討がある程度可能なことから徐々に一般化しつつある．ところが，最近R-CHOPで治療されたDLBCLではDLBCL亜型の予後がCHOP時代とは異なることが報告された．Nymanらはrituximab併用化学療法および化学療法のみで治療されたDLBCLについて免疫組織学的にDLBCL亜型解析を行い予後との関連について解析した[10]．化学療法のみで治療された場合はGCBに比べてnon-GCBの予後が不良だったが，rituximab併用化学療法で治療された場合はGCB, non-GCBの予後には差がなかった(図4)．同様の結果は2006年の米国血液学会においてBritish Columbiaからも報告されており[11]，DLBCL亜型はR-CHOP時代においては予後にインパクトを与えないことが明らかとなった．

DLBCL亜型以外にもrituximab導入前に同定された生物学的予後因子でもR-CHOP時代には予後因子とならない場合があることが報告されている．Bcl-2過剰発現はrituximab時代以前にはaggressive lymphomaの予後不良因子として報告された[12][13]．しかしR-CHOPで治療されたDLBCLではBcl-2過剰発現は予後因子とならない[14]．Bcl-6タンパク発現はgerminal center由来B細胞の指標であり，化学療法のみで治療されたDLBCLにおいては予後良好因子であることが報告されている[15]．しかしR-CHOPで治療されたDLBCLにおいてはBcl-6タンパク発現の有無は予後に影響を与えない[16]．一方，われわれはp53遺伝子変異がaggressive lymphomaの予後不良因子であることをrituximab時代以前に明らかにした[17]．p53遺伝子変異はDLBCLに限った場合でも有意な予後因子であるが[18]，R-CHOP時代においてもp53遺伝子変異と相関するp53タンパク過剰発現が予後不良因子となることが報告された(図5)[19]．

このように，rituximab時代以前に同定されたDLBCLの生物学的予後因子はR-CHOP時代には意義が変化するものがあり，今後再評価が必要になるとともに新たな生物学的予後因子を探索する必要がある．

DLBCLに対する至適治療

DLBCLに対する標準的化学療法としてはR-CHOP療法が確立したが，至適治療を考える上では年齢，臨床病期，予後因子といったさまざまな要因を考慮する必要がある．また放射線治療

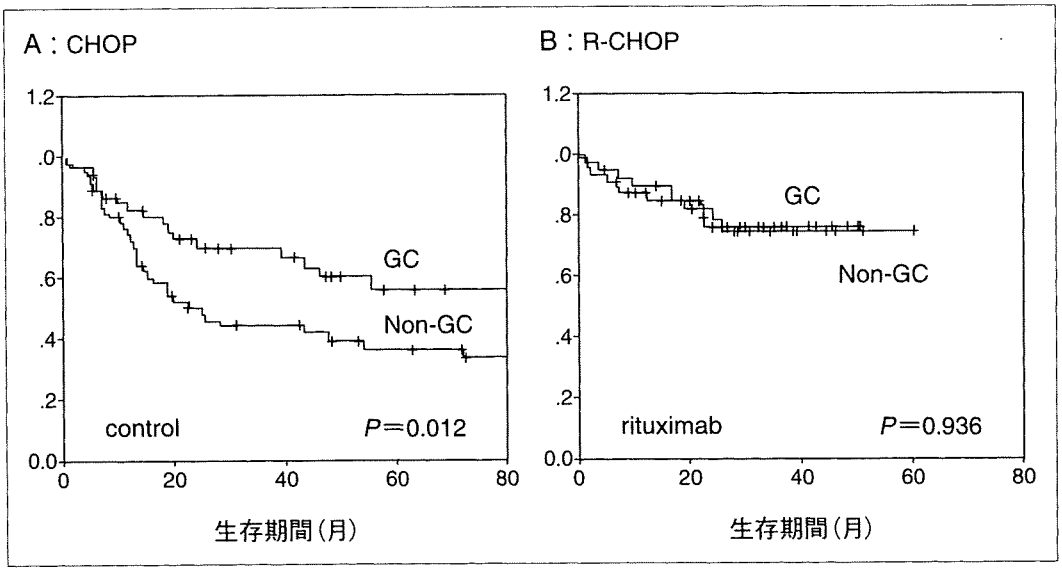

図4　免疫組織学的に同定されるDLBCL亜型の治療成績
A：CHOP-like chemotherapyで治療されたDLBCL，B：rituximab併用CHOP-like chemotherapyで治療されたDLBCL．GC：germinal center type DLBCL，Non-GC：non-GC DLBCL．Rituximab併用化学療法で治療された場合にはGC, non-GCの予後に差がない．　（文献[10]より引用改変）

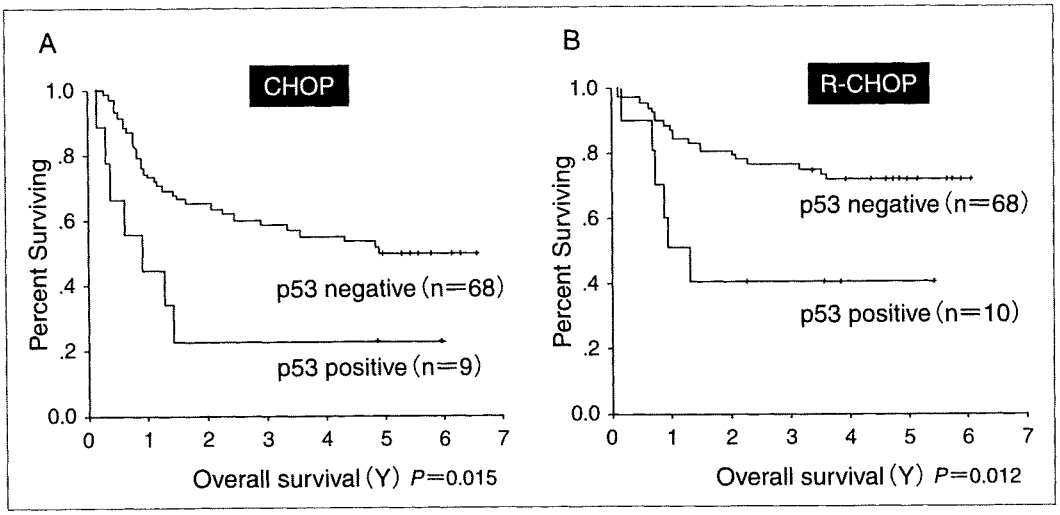

図5　p53タンパク発現とDLBCLの予後
A：CHOPで治療されたDLBCL，B：R-CHOPで治療されたDLBCL．いずれにおいても免疫組織学的に検出されるp53タンパク高発現は予後不良因子である．　（文献[19]より引用改変）

の併用，R-CHOP療法のコース数，G-CSFを併用したdose intensified chemotherapyの意義，さらには造血幹細胞移植併用大量化学療法の位置づけなどについて考慮する必要がある．以下いくつかの視点から至適治療について考察してみたい．

1．年　齢

進行期高齢DLBCLに対するR-CHOP療法では，GELAの報告では80歳までを対象としてR-CHOP療法を8コース施行している．Cyclophosphamide, doxorubicin, vincristineの投与量は標準的CHOPと同様だが，prednisoloneについては100mg/bodyではなく40mg/m^{2}で投与された．ドイツから報告されたRICOVER-60ではR-CHOPは6コース(CHOPは6コースだが，rituximabは8回投与されている)が至適治療と報告された．ただしこれはG-CSF併用により2週間隔で行われるCHOP-14療法がベースになっているため，3週ごとに行う標準的CHOPにもあてはまるかどうかは不明である．現在GELAでは，高齢DLBCLを対象に3週

ごとに行うR-CHOP-21と2週ごとに行うR-CHOP-14のランダム化比較試験が行われており，この結果が待たれる．なお，ASCOのCSF使用に関するガイドラインに示されているとおり，高齢者DLBCLに対する化学療法ではG-CSFを予防的投与することが望ましい[20]．

若年者についてはMinT studyの結果などから高齢者と同様にR-CHOP療法が標準的治療として位置づけうると考えられる．MinTではR-CHOPは6コース施行されたが，これがhigh risk群を含めた若年者一般に適応しうるかどうかは不明であり，現時点ではR-CHOP-21 8コースが標準的治療と考えられる．

2．限局期DLBCL

限局期aggressive lymphomaに対してはCHOP 3コースと病変部に対する放射線治療の併用療法（CHOP×3＋IF-RT）がCHOP 8コースに勝ることが報告されてからCHOP×3＋IF-RTが標準的治療とされている[21]．ただし，この試験の長期観察の結果では7年EFSや9年OASでは差を認めなかった．これはリンパ腫再発による晩期死亡がCHOP×3＋IF-RT群で多かったためとされる．その後，GELAで60歳以下の限局期aggressive lymphomaを対象としたCHOP×3＋IF-RTと治療強度を高めた併用化学療法であるACVBP療法との比較試験が行われ，ACVBP療法が勝ることが報告された[22]．また，同じくGELAからIPIでの予後不良因子をもたない高齢者限局期aggressive lymphomaを対象としたCHOP×4＋IF-RTとCHOP×4の比較試験結果が報告され，CHOPと放射線併用療法はCHOP単独に勝らないとされた[23]．

以上はすべてrituximab導入以前に行われた研究である．現在では進行期DLBCLについてはR-CHOPが標準的治療として確立したことから，限局期DLBCLに対してもR-CHOPが至適化学療法と考えられる．今後R-CHOPへの放射線併用の有用性やR-CHOPの至適コース数に関する検討が必要である．

3．IPI高リスク群

予後不良aggressive lymphomaの治療成績を改善する目的で自己造血幹細胞移植併用大量化学療法の臨床試験が数多く施行されている．その対象としてはIPIでのhigh-intermediate riskおよびhigh riskが適切とされる[24]．これまでの報告では自己造血幹細胞移植併用大量化学療法の有用性を認めたとするもの[25][26]と，認められなかったとするものがある[27][28]．このように，初発aggressive lymphomaに対する自己造血幹細胞移植併用大量化学療法の有用性は十分には確立していない．とくにrituximab導入後のDLBCLに対する大量化学療法に関する成績は乏しいこともあり，臨床試験による検証が必要である．

今後の課題

このように，rituximabによってDLBCLの治療成績は大きく向上したが，いまだ治癒が得られない患者も多く，予後不良患者に対する治療はさらなる改善が求められている．今後，R-CHOP療法の効果が不十分な患者の病態解明とR-CHOP時代における予後因子の確立，大量化学療法の位置づけやrituximabの投与スケジュールなど至適使用方法に関する検討が重要と考えられる．

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Clinical validity of the Japanese version of the Functional Assessment of Cancer Therapy-Anemia Scale

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Abstract *Goals of work:* The purpose of this study was to reveal the clinical validity of the Japanese version of the Functional Assessment of Cancer Therapy-Anemia scale (FACT-An) in relation to hemoglobin level. We also analyzed patients' scores for the related FACT-General scale (FACT-G), the FACT Anemia subscale, and the FACT Trial Outcome Index-Anemia scale (FACT TOI-An) to determine which was the most sensitive to anemia measurements. *Materials and methods:* Throughout Japan, we recruited 227 patients (mean±SD, 59±12.1 years old) diagnosed with a variety of cancers. We correlated the severity of anemia, as measured by hemoglobin levels, to scores on the FACT-An and on the other scales at baseline and at 3 months. *Main results:* The questionnaire completion rate was more than 98% at both time points. The FACT-An had high internal consistency (Cronbach's alpha coefficient >0.8). FACT-An scores were significantly and positively correlated with hemoglobin levels both at baseline (r=0.24; 95% CI=0.12 to 0.36; n=225) and at 3 months (r=0.24; 95% CI=0.10 to 0.36; n=204). FACT-G, FACT Anemia subscale, and FACT TOI-An scores also successfully discriminated between patients with lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels. Moreover, the changes of these FACT scores over 3-months could discriminate changes in hemoglobin level. *Conclusion:* The Japanese version of the FACT-An has higher clinical validity and can be used to appropriately assess health-related quality of life among Japanese cancer patients with anemia.

Keywords Cancer · Anemia · Validity · Quality of life · Functional Assessment of Cancer Therapy

Introduction

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System [2] includes several patient-completed questionnaires that contain more than 250 questions. It was developed to measure health-related quality of life (HRQOL) of patients with cancer and other chronic illnesses. The FACIT has been translated into more than 40 languages.

The Functional Assessment of Cancer Therapy-General scale (FACT-G) [2] is the core questionnaire of the FACIT system. It contains four subscales to assess major HRQOL domains such as physical, social, emotional, and functional concerns of patients with specific health problems. The Japanese version of the FACT-G was developed and validated by Fumimoto et al. [6] in 2001.

The FACT-Anemia scale (FACT-An) [1] consists of FACT-G plus Anemia subscale to assess anemia-related HRQOL concerns and was developed in 1994. The Japanese version of the FACT-An was validated by Yoshimura et al. [10] in 2004.

To validate FACT-An, Yoshimura et al. examined test–retest reliability, factorial validity, construct validity, and internal consistency. However, the design of the study was cross-sectional; clinical validity was defined only with correlations to performance status ratings: the important clinical indicator for anemia, hemoglobin level, was not used, and the sample included only lung cancer patients. In this study, we examined the clinical validity of the Japanese version of the FACT-An in relation to hemoglobin level (1) among a larger group of patients, (2) receiving various treatments for a range of cancers, and (3) at two time points of 3 months apart.

Materials and methods

The Functional Assessment of Cancer Therapy-Anemia scale (FACT-An)

The FACT-An is an extension of the FACT-G questionnaire. The FACT-G consists of a core set of 27 generic QOL questions. The core questions measure four major aspects of QOL: physical well-being (PWB, seven items), social–family well-being (SWB, seven items), emotional well-being (EWB, six items), and functional well-being (FWB, seven items). The FACT-An consists of these four FACT-G subscales and a 20-item FACT Anemia subscale. Of the 20-item FACT Anemia subscale items, 13 relate to fatigue [1]. Each FACT-An item is scored on a 0-to-4-point Likert scale, giving a range of scores from 0 to 188. Higher scores indicate better HRQOL.

The FACT Trial Outcome Index-Anemia (FACT TOI-An) is a scale that includes the PWB subscale and the FWB subscale, from the FACT-G, and the Anemia subscale. This scale was developed exclusively for clinical trials of anticancer drugs, in which physical and functional domains and symptoms were thought to be more important than emotional and social domains. Total scores of FACT TOI-An range from 0 to 136. In addition to testing the validity of the FACT-An questionnaire, we determined which of the scales (FACT-G, FACT-An, Anemia subscale, or FACT TOI-An) was the most sensitive to anemia as defined by hemoglobin levels.

Patients

Patients were recruited from eight hospitals throughout Japan. All of them spoke Japanese and were asked to complete the questionnaire at baseline and at 3 months.

The study included patients who were receiving, or who were planning, to receive cancer treatment. Treatments included chemotherapy, hormonal therapy, radiation therapy, or a combination. Patients who had surgical treatment were not included, but patients who received adjuvant treatments 3 months after the surgery were included. Epoetin alpha was not used for these patients as the drug is not approved in Japan.

Other inclusion criteria were: age older than 20 years old, an Eastern Cooperative Oncology Group Performance Status of 0 to 2, creatinine level $\leq$2.0 mg/dl, and expected survival of 3 months or more. Patients who had hemorrhagic lesions or nontreatment-related anemia, such as iron deficiency anemia or hemolysis, were excluded. Patients who were unable to participate in the study because of unfavorable health conditions, as suggested by the physician, were also excluded.

Demographic, disease, and treatment information were gathered from clinical records. All patients gave written informed consent after receiving a thorough verbal explanation of the protocol. The study conformed to the principles in the Declaration of Helsinki and was approved by the ethics committee of each institution.

Statistical methods

Data collection, management, and monitoring were coordinated by the Comprehensive Support Project for Oncological Research (CSPOR) data center of The Japan Clinical Research Support Unit (J-CRSU).

To examine the clinical validity of the HRQOL questionnaire, FACT-An scores were correlated with patients' hemoglobin measurements at baseline and at 3 months using Pearson's correlation coefficient. We also analyzed the data by FACT-G, Anemia subscale, and FACT TOI-An scores.

Internal consistency was determined by Cronbach's alpha coefficient. Factor analysis using Promax rotation was used to confirm the subscale structure of the FACT-An scale.

Table 1 Baseline demographic and clinical characteristics of 227 cancer patients participating in a validation study of the Functional Assessment of Cancer Therapy-Anemia scale

Characteristic	Mean±SD (range)	Patients	
		n	Percentage
Age, years	59.0±12.1 (27 to 84)		
Sex			
Male		126	55.5
Female		101	44.5
Cancer-related complications			
Yes		77	33.9
No		150	66.1
Cancer type			
Lung		98	43.2
Breast		60	26.4
Stomach		3	1.3
Colon		4	1.8
Liver, bile, pancreas		3	1.3
Lymphoid gland		32	14.1
Leukemia		24	10.6
Others		3	1.3
Hemoglobin levels (g/dl)	11.4±1.8 (4.5 to 15.6)		
<11.0		92	40.5
<8		13	5.7
8–9		6	2.6
9–10		25	11.0
10–11		48	21.1
≥11.0		135	59.5
11–12		38	16.7
12–13		60	26.4
>13		37	16.3

Severe anemia was defined as a hemoglobin level <11.0 g/dl [5]. We tested the ability of the eight FACT scales to discriminate between patients with lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels using Student's *t* test. First, the ability of FACT scales to discriminate patients between these two ranges of anemia was examined in the two assessment points. Next, simple regression analysis was used to determine the relationship between changes in QOL scores and changes in hemoglobin levels over 3 months. Linearity was assessed with an analysis of residuals.

All missing values were treated according to the FACT scoring instructions. All analyses were performed with SAS for Windows, version 8.02; (SAS Institute, Cary, NC, USA). *P* values less than 0.05 were considered to be statistically significant unless indicated otherwise.

Results

Between October 2003 and May 2004, 227 patients were recruited. At baseline, the rate of patients completing the questionnaire was 99.1% (225/227). At 3 months, 18 had dropped out. Reasons included voluntary withdrawal (n=2), transfer to another hospital (n=2), death (n=10), and others (n=4). Of the remaining 209 patients, 204 (97.0%) completed the questionnaires. For each item in the questionnaire, the frequency of missing data was less than 2% at baseline and less than 4% at 3 months, except for item 16 of FACT-G scale which asked about sexual satisfaction; this question went unanswered in 51.5 and 54.1% of the questionnaires at baseline and at 3 months, respectively. Demographic data and HRQOL scores did not show any difference except for cancer type and treatment method.

The sample represented a broad spectrum of cancer diagnoses (Table 1). About 40% of the patients had the lower range of hemoglobin level (Hb<11.0 g/dl) at baseline. The mean (SD) hemoglobin levels at baseline (11.4±1.8) and at 3 months (11.4±1.7) were not different. However, at 3 months, values were improved in 41% of patients (n=86), unchanged in 21% (n=43), and worse in 38% (n=80).

Validation

FACT-An scores were correlated with hemoglobin levels both at baseline (r=0.24, 95% CI=0.10 to 0.36; n=225) and at 3 months (r=0. 24, 95% CI=0.10 to 0. 36; n=204).

All the subscales of the FACT-An had high internal consistency. At baseline, Cronbach's coefficient alpha was between 0.79 and 0.84 for each domain of the FACT-G and

Table 2 Validation characteristics for the HRQOL scales

Scale	Baseline scores (n=227)			3-Month scores (n=209)		
	Mean	SD	Cronbach's alpha	Mean	SD	Cronbach's alpha
FACT-G (27 items); scores range from 0 (low) to 108 (high)	70.8	14.7	0.86	70.1	15.1	0.87
FACT-An (47 items); scores range from 0 (low) to 188 (high)	126.3	25.0	0.92	125.6	26.5	0.93
Anemia subscale (20 items); scores range from 0 (low) to 80 (high)	55.6	12.9	0.90	55.4	14.0	0.92
FACT TOI-An (34 items); scores range from 0 (low) to 136 (high)	91.8	21.3	0.93	91.5	22.9	0.94

HRQOL Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia

Table 3 Ability of HRQOL scales to discriminate between patients with lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels at baseline

Scale	Degree of anemia at baseline					
	Hb <11.0 g/dl		Hb ≥11.0 g/dl		*F*	*P*
	n	mean (SD)	n	mean (SD)		
FACT-G	91	67.5 (14.4)	134	73.0 (14.6)	7.92	0.005
FACT-An	91	120.2 (24.9)	134	130.5 (24.3)	9.39	0.003
Anemia subscale	92	52.6 (13.3	135	37.2 (9.2)	8.51	0.004
FACT TOI-An	92	86.0 (21.6)	135	95.7 (20.2)	11.92	<0.001

HRQOL Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia

0.90 for the Anemia subscale. At 3 months, Cronbach's coefficient alpha was between 0.82 and 0.86 for each FACT-G domain and 0.92 for the Anemia subscale (Table 2). These results indicate that items in each domain or scale measured a unidimensional concept. Factor analysis also showed good factor validity for FACT-An (data not shown.)

All HRQOL subscales used in this study differentiated anemia appropriately, where higher QOL scores were associated with higher hemoglobin levels (Tables 3 and 4). FACT TOI-An discriminated anemia most efficiently both at baseline and at 3 months.

Simple regression analyses showed that changes in scale scores over 3 months correlated linearly and positively with changes in hemoglobin level. The results suggest that these HRQOL scales are sensitive to changes over time (Table 5).

Discussion

Anemia is an important concern when treating cancer patients. Interventions to reverse fatigue and anemia using growth factors, such as epoetin alfa, have shown benefits in Western countries [4, 5, 7, 9]. These interventions have not been studied in Japanese patients, and these drugs have not been approved in Japan. Therefore, we did not use any of these drugs for our study. Developing a reliable and valid scale to properly measure HRQOL in Japanese cancer patients with anemia is important to conducting such studies.

We validated the FACT-An in cancer patients by its feasibility, reliability, and factor validity and revealed the clinical usefulness of FACT-An in discriminating the severity of anemia as measured by hemoglobin levels. Our results showed that the FACT-An and the Anemia subscale in Japanese version were clinically valid instruments for measuring the subjective symptoms of anemia and other general HRQOL aspects among patients with different cancers.

A previous validation study [1] defined anemia with different hemoglobin levels. We set 11 g/dl as the cutoff point for lower or higher levels of anemia in cancer patients. The greatest change in HRQOL scores occurred in patients with hemoglobin levels between 11.0 and 13.0 g/dl. Crawford et al. [5] showed that when Linear Analog Scale Assessment was plotted against hemoglobin level on a sigmoid curve, the steepest slope of HRQOL curve was seen at around 11.0 g/dl. Moreover, we consider 11.0 g/dl a clinically valid value to define anemia, especially when examining both men and women together.

When conducting the current study, the purpose and method of this study were explained by nurses and clinical staff. With that, we achieved excellent completion rate for almost all items (more than 98%). On the other hand, item

Table 4 Ability of HRQOL scales to discriminate between patients with lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels at 3 months

Scale	Degree of anemia at 3 months					
	Hb <11.0 g/dl (*n*=92 patients)		Hb ≥11.0 g/dl (*n*=135 patients)		*F*	P
	n	Mean (SD)	*n*	Mean (SD)		
FACT-G	72	67.8 (14.6)	132	77.3 (15.3)	2.45	0.119
FACT-An	72	120.1 (25.2)	132	128.6 (26.9)	4.85	0.030
Anemia subscale	75	52.1 (13.8)	132	37.3 (10.3)	6.95	0.009
FACT TOI-An	75	85.1 (22.4)	132	95.0 (22.5)	9.28	0.003

HRQOL Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia

Table 5 Regression coefficients for predicting changes in HRQOL scores from changes in hemoglobin levels over 3 months

Scale	Regression coefficient	95% CI	r^2	*P*
FACT-G	0.18	0.05–0.31	0.0340	0.007
FACT-An	0.23	0.09–0.35	0.0517	0.002
Anemia subscale	0.22	0.08–0.34	0.0472	0.002
FACT TOI-An	0.22	0.09–0.34	0.0479	0.004

HRQOL Health-related quality of life, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACT-An* Functional Assessment of Cancer Therapy-Anemia, *FACT TOI-An* Trial Outcome Index-Anemia, *95% CI* 95% confidence interval for the regression coefficient (the slope of the regression line), r^2 Coefficient of determination; as a measure of predictive ability of the regression model, it indicates the proportion of the variability in changes in hemoglobin levels, which is explained by knowing the change in HRQOL scores

16 of FACT-G had the highest nonresponse rate both at baseline and at 3 months. Item 16 asked about "sexual satisfaction with one's partner". We believe that the high nonresponse rate for this item is related to the Japanese culture. The similar nonresponse rate was seen in previous studies of the same instrument in Japan [8].

We described whether changes in hemoglobin level predicted changes in QOL scores over 3 months in our study. We must note, however, that the *r*-square values for all scales are small in our analysis. QOL is greatly influenced by a variety of individual factors such as personal social events or individual understanding of HRQOL. As hemoglobin level is just one of such factors, using only hemoglobin level as a clinical indicator to explain or predict QOL variation has its limitation. In our study, we only showed that a change in hemoglobin level could be a predicting factor of QOL because it was one of the statistically significant explanatory factors.

FACT TOI-An is a scale that measures HRQOL related to the physical and functional domains, as well as anemia. Our study showed that FACT TOI-An best differentiated the anemic status of cancer patients categorized into lower (Hb <11.0 g/dl) and higher (Hb ≥11.0 g/dl) hemoglobin levels when compared with other scales. When Cella et al. [3] validated HRQOL measures of lung cancer patients using the FACT-L, they constructed the 21-item TOI-L by combining the scores of PWB and FWB. The Cronbach's alpha for the TOI-L was high, suggesting that little information was lost when combining the domains and subscales into one. They showed that TOI was the most precise indicator of patient-reported HRQOL for lung cancer patients in a clinical trial. In contrast to Cella's result, the change seen in our study was small. This is because the PWB condition of patients at baseline influences the scores of FACT TOI-An to a great extent. Because our study was noninterventional, we would expect an interventional study using FACT-An to show a larger difference.

Conclusions

The Japanese version of the FACT-An has higher clinical validity and can be used to appropriately assess HRQOL among Japanese cancer patients with anemia.

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Case Report

Successful Treatment of Advanced Extranodal NK/T Cell Lymphoma with Unrelated Cord Blood Transplantation

HISAYUKI YOKOYAMA,[1] MINAMI F. YAMADA,[1] KENICHI ISHIZAWA,[1] JOJI YAMAMOTO,[1] YASUO TOMIYA,[2] HIDEO HARIGAE,[1] JUNICHI KAMEOKA,[1] RYO ICHINOHASAMA[2] and TAKESHI SASAKI[1]

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YOKOYAMA, H., YAMADA, M.F., ISHIZAWA, K., YAMAMOTO, J., TOMIYA, Y., HARIGAE, H., KAMEOKA, J., ICHINOHASAMA, I. and SASAKI, T. *Successful Treatment of Advanced Extranodal NK/T Cell Lymphoma with Unrelated Cord Blood Transplantation.* Tohoku J. Exp. Med., 2007, **211** (4), 395-399 —— Nasal natural killer (NK)/T cell lymphoma is a rare entity of non-Hodgkin's lymphoma which mostly occurs in East Asian countries. The advanced disease above clinical stage III is often refractory to the radiation and chemotherapies, remission is transient even if achieved, and median survival is about 12 months. Thus the prognosis of advanced NK/T cell lymphoma is generally poor, however, the promising results of allogeneic hematopoietic stem cell transplantation for advanced NK/T cell lymphoma have been recently reported. In most of these cases, stem cell sources were human leukocyte antigen (HLA) matched donors and alternative sources were seldom used. We report here a case of a 36-year-old woman who was diagnosed as having an extranodal NK/T cell lymphoma, nasal type. The patient achieved a complete remission after 2 cycles of chemotherapy including Carboplatin, Etoposide, Ifosfamide, and Dexamethasone, but 3-months later relapsed during the search for HLA-matched unrelated donors. She received unrelated cord blood transplantation (CBT) in the second remission achieved by a regimen containing L-asparaginase. The conditioning regimen was 12 Gy of total body irradiation, high-dose cytarabin and cyclophosphamide. FK506 and methotrexate were used for graft-versus-host disease (GVHD) prophylaxis. GVHD involving the intestine and the oral mucosa was observed, but improved without additional immunosuppressive therapies. The patient remains in remission 33 months after CBT. Cord blood thus could be an appropriate stem cell source for patients with advanced NK/T lymphoma who have no HLA matched donors. ——— extranodal NK/T cell lymphoma; nasal type; treatment; hematopoietic stem cell transplantation; cord blood

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Natural killer (NK)/T cell lymphoma is a rare entity of non-Hodgkin's lymphoma which mostly occurs in East Asian countries (Cheung et al. 1998; The World Health Organization classification of malignant lymphomas in Japan 2000; Yamaguchi et al. 2001). It is classified into three categories: nasal, non-nasal and aggressive lymphoma/leukemia (Jaffe et al. 1996; Kwong et al. 1997). Nasal NK-cell lymphomas usually occur in nasal cavity and upper aerodigestive tract, and a distant metastasis is infrequent (Nakamura et al. 1997; Wong et al. 2001). Localized disease (clinical stage I, II) has a relatively good prognosis by the therapy including the involved field radiation, 5-year overall survival ranged from 40 to 59% (Kim et al. 2000; Kim et al. 2001; You et al. 2004; Kwong 2005). However, the advanced disease is often refractory to the radiation and chemotherapies, and remission is transient even if achieved, and thus the prognosis is very poor. Complete remission (CR) rate has been shown to be less than 15% and median survival is about 12 months (Nakamura et al. 1997; Kwong 2005). Because of the poor results of chemotherapies for NK/T cell lymphoma, allogeneic hematopoietic stem cell transplantation (HSCT) have been applied to these patients (Murashige et al. 2005). But there were only a few reports describing HSCT for NK/T cell lymphoma and the role of allogeneic-HSCT for NK/T cell lymphoma has not been fully established.

We report here a case of advanced NK/T cell lymphoma, successfully treated by cord blood transplantation (CBT).

Case Report

A 36-year-old Japanese woman was admitted to our hospital because of a nasal obstruction and fever persisting for one month. A physical examination revealed the existence of hepatosplenomegaly. Computed tomography (CT) scan showed tumors in nasal, sinusoidal region (Fig. 1A), and right middle lung area (Fig. 1B) in addition to hepatosplenomegaly. Her laboratory examination showed pancytopenia (WBC 1,000/μl, Hb 9.9 g/dl, Plt 3.2 $\times$ 10^4/μl) and liver dysfunction (ALP 335 IU/l, γ-GTP 100 IU/l, AST 196 IU/l, ALT 104 IU/l). The results of coagulation tests were compatible with disseminated intravascular coagulation (DIC) (PT 51.0%, APTT 66.7 sec, fibrinogen 101 mg/dl, D-dimer 27.7 mg/dl, AT3 76%). Serum lactate dehydrogenase (LDH) was elevated to 4,335 IU/l and soluble interleukin-2 receptor was over 6,334 IU/l. The results of serologic studies for Epstain Barr virus (EBV) were as follows: viral capsid antigen (VCA) IgG $\times$ 320, VCA IgM $\times$ 10, early antigen (EA) IgG $\times$ 10, EB nuclear antigen IgG $\times$ 40. Bone marrow aspiration and biopsy revealed hemophagocytic syndrome and no involvement of abnormal cells. EBV DNA was detected in the bone marrow sample by real time quantitative PCR (RQ-PCR) (2,428 copy/0.2 μg DNA). EBER in situ hybridization of the bone marrow biopsy specimen had not been done, however, the bone marrow involvement was not detected by the pathological examination including immunostaining. The histology of nasal tumor revealed the infiltration of neoplastic lymphoid cells in eosinophilic necrotic background containing nuclear fragments (Fig. 1C). Immunohistochemical staining showed that these neoplastic cells were positive for CD3, CD45, CD56 and negative for CD5, CD10. Several biopsy specimens were collected for flow cytometry analysis, which revealed that these abnormal lymphoid cells were negative for T cell receptor (TCR)α, TCRβ and surface CD3. EBV-encoded small RNA (EBER) was detected in tumor cells by *in situ hybridization* (Fig. 1D). Clonal gene rearrangement of TCR could not be analyzed because of insufficient amount of sample. These findings led to a diagnosis of extranodal NK/T cell lymphoma, nasal type, described by the WHO classification. Her clinical stage was determined as IIIB according to the Ann Arbor staging. An age-adjusted International Prognostic Index (IPI) was defined as high risk.

She received DeVIC chemotherapy, consisting of Carboplatin 300 mg/m^2, etoposide 100 mg/m^2, Ifosfamide 1,500 mg/m^2, Dexamethasone 40 mg/body. After two cycles of DeVIC, she achieved a CR. Since advanced stage NK/T cell lymphoma has been shown to have a poor prognosis, allo-HSCT was planned. But she did not

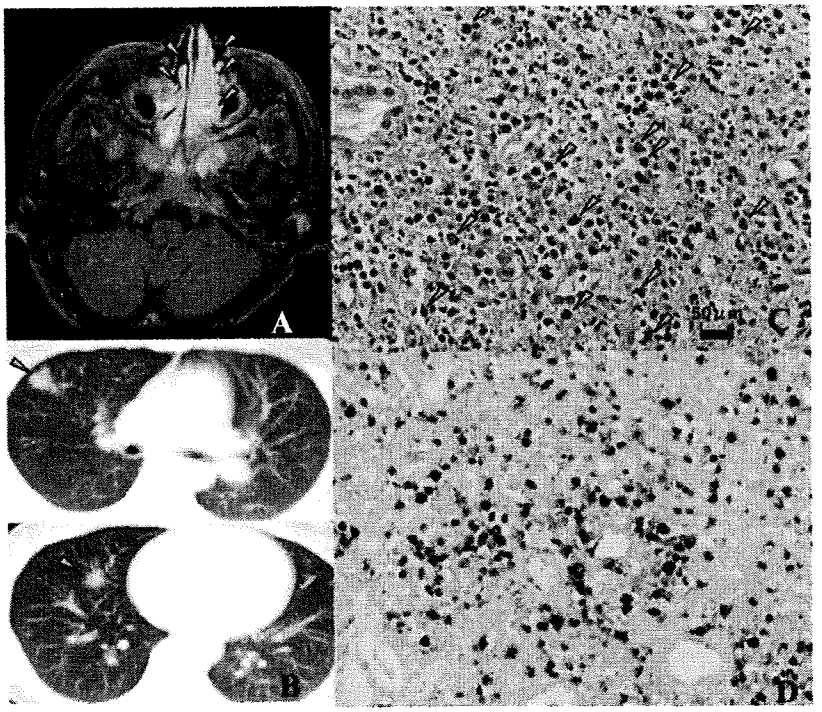

Fig. 1. MRI image, CT image, and histological examination of the lesion.
A: T2-weighted MR image of head. The left nasal cavity and the left paranasal sinus were occupied with tumor showing high signal intensity and enhancement with administration of a contrast medium. The wall of right nasal cavity also showed high signal intensity and enhancement. The tumor was indicated by arrows. B: CT image of lung showing multiple tumors. The tumors were indicated by arrows. C: Hematoxylin and eosin staining of the NK/T cell lymphoma of the nasal cavity showing the infiltration of atypical lymphocytes in necrotic background. The lymphoma cells were indicated by arrows. Clusters of the lymphoma cells were circled. D: EBER *in situ hybridization* of the NK/T cell lymphoma of the nasal cavity. The nuclei of the lymphoma cells were stained in black and positive for EBER.

have either an human leukocyte antigen (HLA)-matched or a partially mismatched related donor, we began to coordinate HLA-matched unrelated donors. RQ-PCR of EBV DNA became negative once. However, after the end of the 4th cycle of chemotherapy, she had a fever again without any signs of infection. Laboratory examination revealed thrombocytopenia ($9.8 \times 10^4/\mu l$) and an elevation of serum LDH (1,032 IU/l). Bone marrow examination showed histiocytic hyperplasia with hemophagocytosis. Although CT scan and MRI did not show apparent tumors besides hyperplasia of nasal mucosa, we made a diagnosis of the recurrence of NK/T cell lymphoma based on clinical and laboratory findings. As a reinduction therapy, L-asparaginase (L-asp) at a dosage of 6,000 U/m^2/day for 7 days, Vincristine (VCR) (1 mg/m^2) and Prednisolone (PSL) (100 mg/body) for one day were administered. After the treatment of L-asp, VCR and PSL, fever resolved and serum LDH level was normalized. Since her remission was expected to be temporary, and an HLA-matched unrelated donor was not available in the Japan Marrow Donor Program, unrelated cord blood transplantation (CBT) was planned.

She was treated with a preparative regimen consisting of total body irradiation (12Gy divided into six fractions on days -9 to -7), Ara-C (2 g/m^2 × 2/day on day -5 and -4) and Cyclophosphamide (60 mg/kg on days -3 and -2). She received a

cord blood unit from a female donor. The number of infused cells and the number of CD34 positive cells before cryopreservation were 2.1×10^7/kg and 0.48×10^5/kg, respectively. The recipient and donor were one-antigen mismatched as defined by serological and DNA typing. As a graft-versus-host disease (GVHD) prophylaxis, tacrolimus (0.015 mg/kg/day) was started on day −1. Methotrexate was administered intermittently (10 mg/m^2 on day 1, 7 mg/m^2 on day 3 and 6). Granulocyte colony stimulating factor was used from day 7. After CBT, the time required to recover neutrophils over 0.5×10^9/l and platelets over 50×10^9/l was 28 and 68 days after CBT, respectively. Acute GVHD of gut (stage 1) and chronic GVHD of oral mucosa appeared on day 55 and day 62 respectively, but resolved without additional immunosupression. She remains in CR for 33 months after CBT with an excellent performance status. The results of RQ-PCR for EBV DNA also remain negative.

Discussion

The treatment for advanced NK/T cell lymphoma generally resulted in poor outcome. Various chemotherapies (Cheung et al. 1998; Kwong et al. 2005) including L-asp (Nagafuji et al. 2001; Yong et al. 2003) and stem cell transplantation have been done to cure these lymphomas; however, there is no established treatment for advanced nasal NK/T cell lymphomas. To date, there are a few reported cases that had underwent allo-HSCT (Teshima et al. 1996; Ohnuma et al. 1997; Takami et al.1998; Tanaka et al. 2001). Recently, the results of 28 patients who had undergone allo-HSCT were reported in a retrospective study (Murashige et al. 2005). Most of 28 patients in this report were advanced disease before HSCT and an overall survival was 40% with a median follow-up of 34 months. These results suggest that HSCT would be a promising treatment for advanced NK/T lymphomas. However, in most of previous reports including the report mentioned above, HLA identical siblings were used for HSCT donors and there were very few report describing NK/T cell lymphoma patients who underwent allo-HSCT using alternative stem cell sources. Recently, cord blood from unrelated donors has been used as an alternative stem cell source for patients who can not have a suitable donor (Laughlin et al. 2004; Rocha et al. 2004). Acceptable results have been published in some hematological malignancies. In regard to NK cell neoplasms, there was only one case report about CBT for blastic NK-cell lymphoma (Yoshimasu et al. 2004), however, the advantage of cord blood, rapid availability, may be attractive as a stem cell source for NK lymphoma, because the appropriate timing for SCT is limited for most of advanced NK lymphoma due to both a short period of CR and a difficulty of controlling the disease. Actually, our case recurred once during the coordination of HLA-identical unrelated donors, and might have missed the appropriate timing of HSCT if it had taken a long time to arrange a stem cell donor in her second remission.

In conclusion, an excellent clinical course of our case suggests that cord blood could be an alternative stem cell source for advanced NK cell lymphoma when patients have no suitable donors. Further accumulation of cases should be needed to clarify this potentiality.

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INTERNAL MEDICINE

□ CASE REPORT □

Aggressive B-Cell Lymphoma with Dual Surface Immunoglobulin Light-Chain Expression

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Abstract

Dual surface immunoglobulin light-chain expression in B-cell malignant neoplasm is a rare event, and has been predominantly reported in chronic lymphocytic leukemia. Herein, we report a case of aggressive B-cell lymphoma with κ/λ-dual surface immunoglobulin light-chain expression of a 69-year-old woman. The lymphoma cells were positive for CD5, CD19, CD20, HLA-DR, Igκ and Igλ. Southern blot analysis confirmed rearranged bands for both light chains with a monoclonal heavy chain rearrangement. She was treated with a combination of rituximab and CHOP regimen, but died of the progressive disease. To our knowledge, this is the first case of aggressive B-cell lymphoma showing dual κ/λ expression; the possible mechanisms of abnormal light chain expression are discussed.

Key words: aggressive B-cell lymphoma, κ/λ dual expression, gene rearrangement

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Introduction

Mature B lymphocytes typically express either κ or λ light-chain, a restriction known as allelic exclusion. Whereas 99.99% of B cells have allelic exclusion at the IgH locus in mice (1), there are few data to draw from to estimate the extent of allelic exclusion at the IgL locus. Indeed, there have been several examples that report on light-chain double producers in normal peripheral B cells as well as in B-cell malignant neoplasms including chronic lymphocytic leukemia (CLL) (2). However, probably because of the limited number of reports available to date, the cellular and molecular mechanisms of dual light-chain expression have not been completely elucidated. Herein, we report a case of B-cell lymphoma with dual surface immunoglobulin light-chain expression, which pursued a clinically aggressive course.

Case Report

A 69-year-old Japanese woman was admitted to our hospital in July 2006 because of high fever and chills persisting for 4 weeks. She had a past history of cerebral infarction. She had massive splenomegaly with no obvious lymphadenopathy. Hematological data was as follows: hemoglobin 7.2 g/dL, platelets 95×10^9/L and white blood cells (WBC) 12.1×10^9/L with 94% neutrophils, 5% lymphocytes, 1% myeloblast. Serum levels of lactate dehydrogenase (LDH), C-reactive protein, soluble interleukin-2 receptor (sIL-2R) and ferritin were 1680 IU/L, 2.1 mg/dL, 9882 U/mL and 2977 ng/mL, respectively. Serum antibody titers did not indicate the presence of autoimmune disease as well as any primary or continuing infection with cytomegalovirus and Epstein-Barr virus. Bone marrow examination disclosed infiltration of abnormal lymphoid cells (15.8% of all nucleated cells) with a high degree of nuclear atypia and distinct nucleoli. Mature histiocytes phagocytosing various hematopoietic cells were also observed. Surface marker analysis of bone marrow mononuclear cells revealed that they were positive for CD5 (55%), CD19 (68%), CD20 (74%) and HLA-DR (72%). Notably, the lymphoma cells were positive for both Igκ (97%) and Igλ (89%) based on a CD19+ gate strategy (Fig. 1A). Rearrangement bands for immunoglobulin heavy chain (JH) and both light-chain genes (Jκ, Cλ) were detected by Southern blot analyses, while only a germline band with decreased intensity was observed when Cκ

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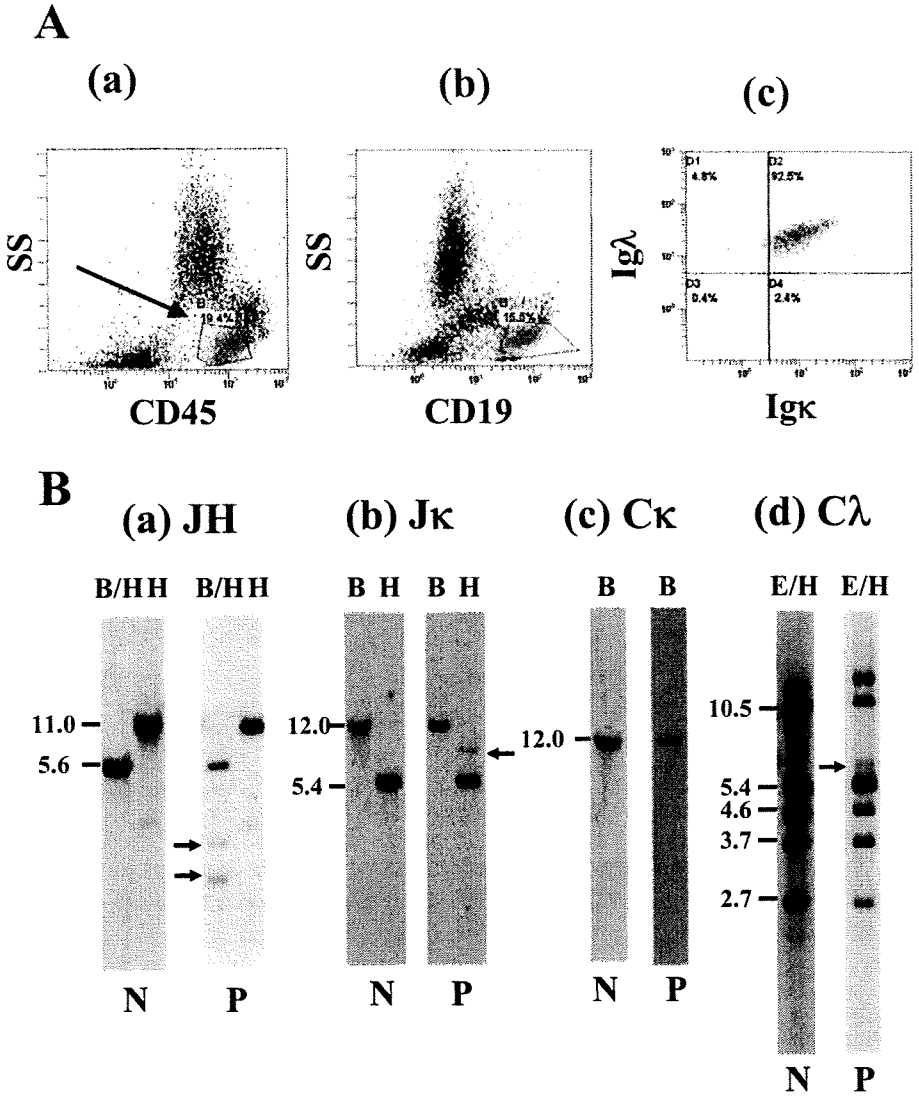

Figure 1. Flow cytometric and genetic analyses of the dual κ/λ-positive lymphoma cells. (A) (a) Bone marrow cells were sorted by a CD45⁺ gate procedure using Cytomics FC 500 (BECKMAN COULTER, Tokyo, Japan) and an abnormal cell population, which showed positivity for CD5 and CD20, was detected (arrow). (b, c) Among them, the CD19⁺ fraction was examined for the expression of Igκ and Igλ. Antibodies recognizing human kappa F(ab')₂ and lambda F(ab')₂ were purchased from BD Biosciences (San Jose, CA, USA). (B) Southern blot analyses of bone marrow cells using probes for immunoglobulin heavy chain (a; JH) and both light-chain genes (b; Jκ, c; Cκ and d; Cλ) are shown. Arrow indicates the rearranged bands. N; normal sample, P; patient sample, B/H; BamHI/HindIII, H; HindIII, B; BamHI, E/H; EcoRI/HindIII.

probe was used for the analysis (Fig. 1B). Cytogenetic analysis of bone marrow cells showed the complex abnormality, with representative karyotype of 46,XX, -1, -1, -2, -3, add (4) (p14), del (7) (q34), -8, add (9) (p13), add (11) (p 11), -14, -14, del (15) (q22), +mar1, +mar2, +mar3, +mar4, +mar5, +mar6, +mar7 (Fig. 2). Thus, she was diagnosed as having B-cell non-Hodgkin's lymphoma associated with hemophagocytic syndrome (HPS). The sites of involvement, clinical features and pathological findings suggested that the lymphoma cell might be categorized into either diffuse large B-cell lymphoma or intravascular large B-cell lymphoma according to the World Health Organization Classification. She was treated with R-CHOP regimen, which initially showed a good clinical response. However, she had the complication of acute cholangitis in September 2006, which was the obstacle in conducting further chemotherapy. In December 2006, the patient relapsed and died of progressive disease.

Discussion

We report a unique case of B-cell lymphoma showing κ/λ-dual expression on the cell surface, with rearrangements in both light chain genes on Southern blot analysis. Although the underlying molecular mechanisms for the generation of κ/λ-positive clones have not been completely elucidated, three assumptions have been suggested to date (2); 1)