療法は，HIV-1感染者では進行例が多いことからABVD (Adriamycin, Bleomycin, Vinblastine, DTIC) やBEACOPPが標準的であり[83]，治療中はHAARTを併用する[84]。Stanford V療法は，骨髄抑制と神経毒性を伴うが，完全寛解率は81％で，標準的治療法よりも生存率も高いと報告されている[85]。

VI. 結　語

エイズリンパ腫の現状と今後の治療戦略について概説した。有効な薬物療法の開発により，AIDSが慢性疾患化した今日，エイズリンパ腫はHIV-1感染者の長期予後を規定する最重要因子となっている。HAART導入により強力な化学療法が可能になり治療がしやすくなったとはいえ，エイズリンパ腫が非エイズリンパ腫と比べて治療に様々な困難を伴うこと，本邦におけるエイズリンパ腫の発症増加が予想されることから[77]，エイズリンパ腫の標準的治療法の確立が必要である。また，エイズリンパ腫の治療には，AIDS特有の合併症やHAARTの副作用などHIV-1感染症への理解が必要であり，血液腫瘍内科医とAIDS治療を専門とする感染症専門医の有機的な連携による集学的治療が重要である。

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SUBNOTE for HIV management

HIV感染者における悪性リンパ腫（AIDS関連悪性リンパ腫）

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AIDS関連悪性リンパ腫はHIV感染者の生命予後を規定する最重要因子の1つ

かつては死の病と言われたAIDS/HIV感染症も、HAARTと呼ばれる強力な抗HIV薬併用療法の導入により予後は劇的に改善した。HAARTによるウイルス増殖の抑制とCD4陽性リンパ球の回復により免疫機能が改善し、日和見感染などで急に命を落とすことが少なくなってきたからである。近年のAIDS/HIV感染症治療の長期化に伴い、HIV感染者の合併症も変化してきている。糖尿病・心疾患などの生活習慣病や肝炎ウイルス感染による肝疾患が増えているとともに、悪性腫瘍の合併がHIV感染者の長期予後を脅かす問題としてクローズアップされてきた。米国の統計では、**HIV感染者は非感染者と比べて悪性腫瘍にかかる率が2倍高い**（表）。また、AIDS指標疾患に属する悪性腫瘍のうち非ホジキンリンパ腫の発症が最も多い。HAART時代に入り、非ホジキンリンパ腫の合併率は減少していると言われているが、AIDS患者10～30%に悪性リンパ腫の合併が認められたとの報告もある。AIDS関連悪性リンパ腫は、治療困難で生命予後が悪いこともあり、今後HIV感染者の生命予後を規定する最重要因子の1つとして位置づけられる。

AIDS関連悪性リンパ腫とは？

悪性リンパ腫は、リンパ系の組織から発生する悪性腫瘍である。リンパ系は、ヒトの免疫系を構成するもので、リンパ節・胸腺・脾臓・扁桃腺などの組織とリンパ節をつなぐリンパ管から成り立つ。悪性リンパ腫はリンパ節を中心に発症するため、**首や腋窩などの体表面のリンパ節が腫れ（リンパ節腫脹）気づくことが多いが、リンパ系は全身に分布しているため、悪性リンパ腫は全身どこでも発生する可能性がある。**

病理学的には、ホジキン病と非ホジキン病に分類され、各々さらに細かく分類されている。悪性リンパ腫は高齢者や腎移植後など免疫機能が低下している人に多いが、HIV感染者では特に発症率が高く重症化することが多い。そのため、原発性脳リンパ腫と非ホジキンリンパ腫は特にAIDS指標疾患の1つに数えられている。HIV感染者の原発性脳リンパ腫の発症にはほぼ100% Epstein-

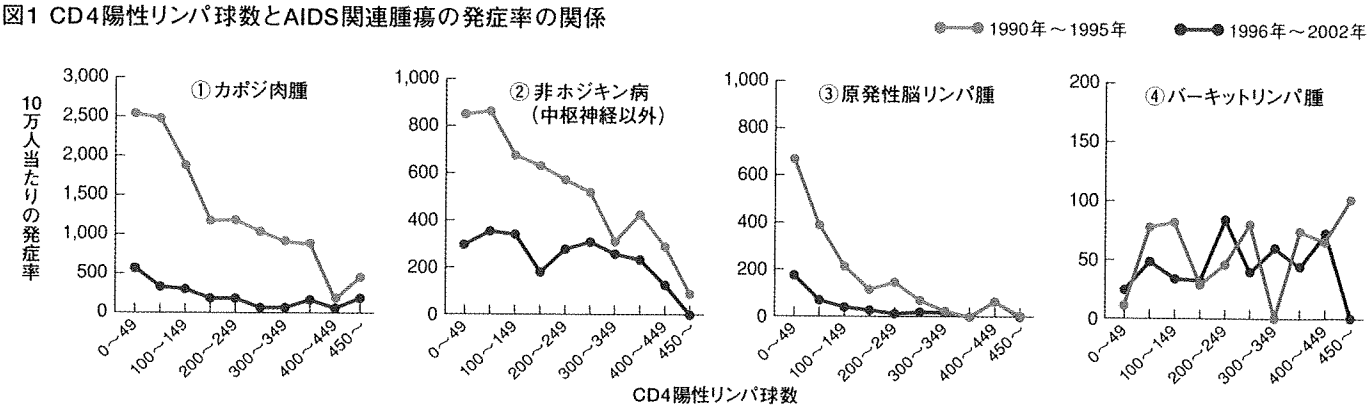
表 米国におけるHIV-1感染者の発癌の危険性

	発症率	Standardized incidence ratio（95%信頼区間）
すべての癌	468/10万人/年	2.0 （2.1 - 2.3）
カポジ肉腫	93/10万人/年	1,300 （1,100 - 1,500）
非ホジキンリンパ腫	109/10万人/年	7.3 （6.4 - 8.4）
原発性脳リンパ腫	15/10万人/年	250 （160 - 360）
浸潤性子宮頸癌	44/10万人/年	2.9 （1.9 - 4.2）

1991年～2002年に登録されたHIV-1感染者57,350人における調査結果。

（Engels EA et al：*Int J Cancer* 123：187-194, 2008より抜粋引用）

図1 CD4陽性リンパ球数とAIDS関連腫瘍の発症率の関係



（Biggar RJ et al：*J Natl Cancer Inst* 99：962-972, 2007より一部抜粋引用）

Barr virus（EBウイルス）感染が関与しており、一部の非ホジキンリンパ腫発症にも関与する。

原発性脳リンパ腫は、カポジ肉腫同様CD4数が落ちているときに発症しやすい。中枢神経以外の非ホジキン病も同様にCD4数が少ない場合に発症しやすいが、その一部であるバーキットリンパ腫はCD4数とは関係なく発症する。HARRT導入以降、CD4数が同じでもカポジ肉腫・原発性脳リンパ腫・非ホジキン病の発症率は減っているが、バーキットリンパ腫の発症率は変わっていない（図1）。また、ホジキン病はAIDS指標疾患ではないが、HIVのコントロール良好な症例に認められ、最近問題になっている。

日本における AIDS関連悪性リンパ腫の推移

HAART以降、世界的にはAIDS関連悪性リンパ腫の合併率は減少しているが、日本においては、AIDS患者数の増加とともにカポジ肉腫と非ホジキンリンパ腫の患者数は増加している（図2）。今後もHIV感染者の増加とともに非ホジキンリンパ腫の患者数の増加が予測され、早急な対策が必要である。永井らの国内の血液研修施設とエイズ拠点病院へのアンケート調査によると、回答のあった349施設中143施設（41%）が2004年から2007年の4年間にAIDS関連リンパ腫を経験しており、その診断と治療に苦慮している（Nagai H et al：*Int J Hematol* 87：442-443, 2008）。AIDS関連悪性リンパ腫の患者は、東京、大阪、名古屋などAIDS患者の多い大都市に多いが、日本全国でみられる。

AIDS関連悪性リンパ腫の治療

非HIV感染者の悪性リンパ腫の治療法は、ほぼ確立している。AIDS関連悪性リンパ腫は、HAART導入以前は日和見感染の合併などにより強力な化学療法ができなかったため、予後不良であったが、HAART以降、全身状態が良好な患者が多くなり強力な化学療法が可能になったことから、治療成績も年々向上している。しかし、AIDS関連悪性リンパ腫は、以下の理由により非HIV感染者の悪性リンパ腫と比べて治療が非常に難しい。

①中枢神経・骨髄・消化管などの節外臓器に発生することが多い。
②初診時にすでに病期が進んでいることが多い。
③HIV感染症・日和見感染症の合併により全身状態の悪い患者が多い。
④抗HIV薬、日和見感染治療薬、リンパ腫治療薬など、多くの薬剤を併用することから、薬剤相互作用による副作用が出やすい。
⑤症例数が少なく比較試験が困難なため、標準的治療法が確立していない。

したがって、AIDS関連悪性リンパ腫の治療にはAIDS/HIV感染症の診療科と血液内科の密な連携が必要となる。また、日本人と西洋人では遺伝学的にさまざまな点で異なるため、欧米における治療方法をそのまま日本人に適応することは難しい。最近、都立駒込病院の味澤篤らにより、**日本人AIDS関連悪性リンパ腫の治療経験に基づいた治療の手引き（味澤 篤ほか：エイズ関連非ホジキンリンパ腫（ARNHL）治療の手引き Ver 1.0. 日本エイズ学会学会誌 11（2）：108-125, 2009）[9]が上梓されたので参考にされたい。**

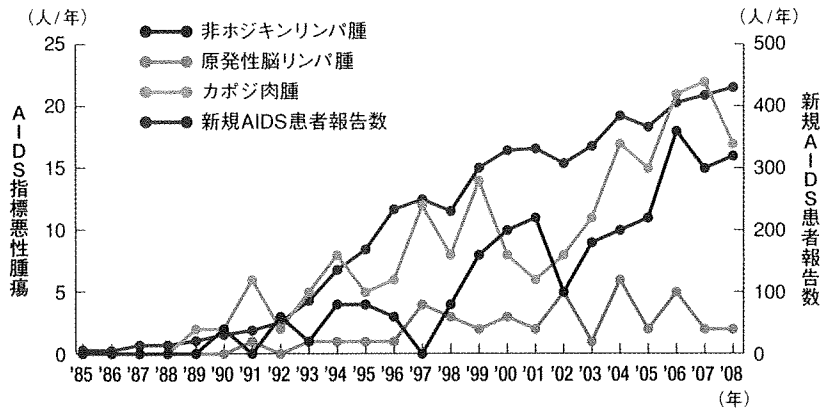
これからの課題

わが国においては、AIDS発症までHIV感染に気がつかない例が約30%に認められる。そのなかで原発性脳リンパ腫や非ホジキン病を初発症状として来院し、HIV感染に気がつかない場合があり注意が必要である。原発性脳リンパ腫と一部の非ホジキン病は、免疫不全に伴うリンパ腫であり、HIV感染症を適切にコントロールしていれば発症予防可能なことから、**HIVの早期発見・早期治療によりAIDS関連悪性リンパ腫の発症を大幅に減らすことができると考えられる。**

一方、**最近、HAARTによりHIV感染症が適切にコントロールされている場合でもリンパ腫が発症することがわかってきているが、その詳細な発症機序は不明であり、今後の研究の成果が待たれる。**

HAART時代に入り、AIDS関連悪性リンパ腫の予後はかなり改善されたが、まだ標準的な治療法の確立には至っていない。また、薬剤の代謝・副作用耐性などに関してはかなりの人種差があることから、今後、日本人に最適化された治療法の確立が必要である。

図2 日本におけるAIDS関連悪性腫瘍の推移



（厚生労働省エイズ動向委員会「平成20年エイズ発生動向年報（平成20（2008）年1月1日～12月31日）」より作成）

9：http://jaids.umin.ac.jp/journal/2009/20091102/20091102108125.pdf

Int J Hematol (2008) 87:442–443
DOI 10.1007/s12185-008-0073-8

LETTER TO THE EDITOR

Actual status of AIDS-related lymphoma management in Japan

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Received: 22 February 2008 / Accepted: 27 February 2008 / Published online: 4 April 2008

Recently, with the widespread use of highly active antiretroviral therapy (HAART), the occurrence of opportunistic infections as an acquired immunodeficiency syndrome (AIDS)-defining illness (ADI) has declined dramatically [1]. Decreases in the incidence of AIDS-related lymphoma (ARL) are not as evident compared with other ADI, so lymphoma has now become one of the most common ADIs [2]. Lymphoma has also become a more common cause of mortality due to AIDS. Management of ARL is starting to represent a critical problem in the total care of the Human Immunodeficiency virus (HIV)-infected population.

In Japan, no epidemiological survey of ARL has been systematically conducted, and the actual status of clinical practice for ARL has been unclear. We therefore made inquiries about ARL management to all hospitals with specialists in hematology (educational hospital certified by the Japanese Society of Hematology) and regional center hospital for HIV/AIDS (502 and 369 institutes, respectively; 209 overlapping institutes) in Japan. First, we asked about experience with ARL treatment and the department responsible for treating ARL in July 2007. Replies were obtained from 305 of the 502 hospitals with specialists in hematology (72.9%) and 218 of the 369 regional center hospitals for HIV/AIDS (59.1%) [174 of 209 overlapping hospitals (83.3%)]. Experience with at least 1 ARL patient was reported by 143 of 349 institutes that responded to our inquiries (41.0%), and ARL was treated in the hematology department in about 80% of these institutes. Next, inquiries about the number of cases of ARL in the past 5 years and treatment modalities for ARL were made to these 143 ARL-experienced institutes. Of the 110 institutes that replied, 54 had treated ARL in the last 5 years (129 cases in total). Of these institutes, 43 treated ARL in the hematology department, and 8 in the infectious disease department (Table 1). These 8 infectious disease departments managed about 40% of all cases of ARL, and thus should be familiar with AIDS and ARL. However, 39 of the 43 hematology departments had experienced less than 2 patients in 5 years, and these institutes also had small numbers of AIDS patients (Table 2). In addition, 40% of ARL cases were treated in these 39 hospitals. The results of this survey suggest the presence of some gap in experience among hospitals treating ARL in Japan.

In the treatment of ARL, use of HAART is considered critical. Clinical studies have shown significant advantages in overall survival when HAART is combined with chemotherapy [3, 4]. However, our survey showed disagreement in the timing of starting HAART among institutes (Fig. 1). The majority of institutes administer chemotherapy against ARL currently with HAART, but 18% of institutes start HAART after completing chemotherapy.

Recently, very high efficacy of dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) for AIDS related aggressive B cell lymphoma was presented [5]. But, the standard chemotherapeutic regimen for ARL has not been established. This study

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Table 1 ARL-treating department

	Institutes	Patients
Hematology department	39	59
Infectious diseases department	8	52
Other	7	18
Total	54	129

The 54 institutes that replied to our questionnaires had treated 129 ARL patients between 2004 and 2007

Table 2 Differences in experience of ARL among institutes

Cases of ARL treated in 1 institute in the last 5 years	≥10	6–9	3–5	1–2
Number of institute treating ARL in hematology department	0	0	4	35
Number of institute treating ARL in infectious diseases department	2	1	2	3
Miscellaneous	0	0	3	4
Total	2	1	9	42

Number of institutes was indicated by the number of ARL cases treated between 2004 and 2007

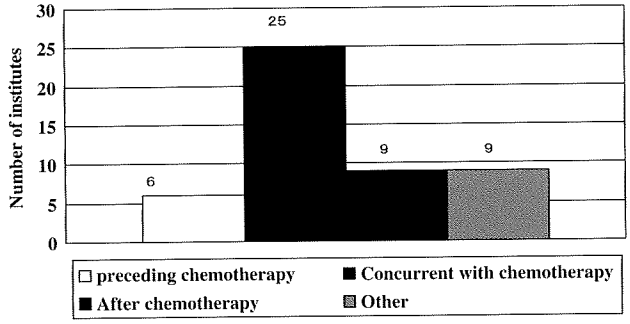

Fig. 1 Start of HAART in treatment of ARL with chemotherapy differs among institutes. A total of 49 institutes replied to this questionnaire

showed that chemotherapeutic regimens have not been standardized also in Japan. At the treatment for AIDS-related diffuse large B-cell lymphoma (DLBCL), the majorities of institutes have adopted EPOCH or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy. As indicated in this study, the combination of rituximab remains controversial for AIDS-related B-cell lymphoma (Fig. 2) [6, 7]. The addition of rituximab to chemotherapy improved the response rate, but increased the risk of infectious events. Rituximab should be used cautiously especially in low CD4 counts patients [8].

As shown earlier, management of ARL is inconsistent among institutes, and probably among individual doctors.

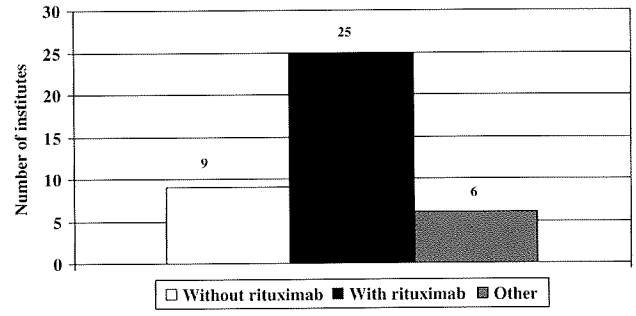

Fig. 2 Rituximab is not uniformly used for AIDS-related DLBCL (institutional policy). A total of 40 institutes replied to this questionnaire

Provision of appropriate guidelines for ARL treatment, including HAART, chemotherapeutic regimens and supportive care, thus seems important and urgent. A nationwide cooperative system of approaching ARL between hospitals, including epidemiological research, performance of clinical trials and consultation with patients needs to be established. Such steps would significantly contribute to the clinical care of ARL patients and might finally improve the quality of medication for the HIV-infected population in Japan.

Acknowledgments This work was supported by a Health and Labour Sciences Research Grand from the Ministry of Health, Labour, and Welfare of Japan (Grant number: H19-AIDS-003).

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bjh research paper

Remission induction therapy containing rituximab markedly improved the outcome of untreated mature B cell lymphoma

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Received 29 May 2008; accepted for publication 23 July 2008

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Summary

Many controlled clinical trials have proven that rituximab improves the clinical outcome of patients with mature B cell lymphoma. This study was conducted to assess the contribution of rituximab in the actual clinical practice. Patients with newly diagnosed mature B cell lymphoma treated at 20 National Hospital Organization hospitals from January 2000 to December 2004 were consecutively registered. Rituximab was approved in September 2002 for indolent B cell lymphoma and in September 2003 for aggressive B cell lymphoma in Japan. The patients were divided into two groups depending on whether they received induction therapy containing rituximab. The endpoint was to evaluate the rituximab benefit based on 2-year progression-free survival (PFS) and 2-year overall survival (OS). A total 1126 patients received chemotherapies. Of these, 762 were diagnosed as diffuse large B cell lymphoma (DLBCL) and 215 as follicular lymphoma (FL). PFS and OS were markedly improved in the rituximab group compared with the non-rituximab group in patients with DLBCL (both $P < 0{\cdot}001$) and in patients with FL ($P < 0{\cdot}001$ and $P = 0{\cdot}003$ respectively). Rituximab, when used for remission induction therapy, significantly improved the clinical outcome of the mature B cell lymphoma patient in actual clinical practice.

Keywords: rituximab follicular lymphoma, diffuse large B cell lymphoma, clinical practice.

Non-Hodgkin lymphoma (NHL) is one of the leading causes of cancer death, and its incidence is increasing. The majority of NHL has a B cell phenotype. Almost all B cell lymphomas express CD 20 antigen on the cell surface. Rituximab, a chimeric anti-CD20 monoclonal antibody, was developed and is now widely used to treat B cell lymphoma. Many clinical

First published online 20 October 2008
doi:10.1111/j.1365-2141.2008.07390.x

studies have established the effect of rituximab against B cell lymphoma (MacLaughlin *et al*, 1998; Czuczman *et al*, 1999, 2004; Coiffier *et al*, 2002; Forstpointner *et al*, 2004; Hiddemann *et al*, 2005; Lenz *et al*, 2005; Marcus *et al*, 2005; Rivas-Vera *et al*, 2005; Habermann *et al*, 2006; van Oers *et al*, 2006; Pfreundschuh *et al*, 2006, 2008; Herold *et al*, 2007). The toxicity of rituximab has been generally graded as 1 or 2, and it occurs with the first infusion (MacLaughlin *et al*, 1998); the safety of rituximab when combined with chemotherapy has been shown to be similar to that of chemotherapy alone. Randomized phase III studies have proven the survival benefits of the addition of rituximab to multi-agent chemotherapy for patients with untreated follicular lymphoma (FL) (Hiddemann *et al*, 2005; Herold *et al*, 2007) and those with untreated diffuse large B cell lymphoma (DLBCL) (Coiffier *et al*, 2002; Pfreundschuh *et al*, 2006, 2008;). A systematic review also showed the clinical impact of rituximab for low-grade B cell lymphoma (Schulz *et al*, 2007). These data demonstrated that rituximab has an indisputable benefit for patients with untreated and relapsed/refractory B cell lymphoma who were enrolled in well controlled clinical studies. One population-based retrospective analysis by the British Columbia Cancer Registry assessed the effect of rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) for DLBCL and demonstrated improvement in treatment outcome (Sehn *et al*, 2005). This survey revealed that rituximab contributed to the management of DLBCL in clinical practice. However, the cases studied were restricted to those with DLBCL who received CHOP (with/without rituximab) with curative intent. Therefore, no study has reported the clinical benefit of rituximab in patients with B cell lymphoma in actual clinical practice. To address this point, a retrospective survey comparing patients with B cell lymphoma treated with and without rituximab was conducted. The results showed remarkable improvement in the survival of patients with FL and those with DLBCL, which account for the majority of mature B cell lymphoma patients, by the addition of rituximab in actual clinical practice.

Patients and methods

This was a retrospective cohort study that examined the clinical outcome of all untreated patients with B cell lymphoma who visited the haematological department of 20 hospitals belonging to the National Hospital Organization (NHO), a major, nationwide hospital group in Japan, from January 2000 to December 2004. This research group was founded for the purpose of creating and generalizing clinical evidence in the haematological field by NHO and is called the Clinical Hematology Group of NHO (CHG–NHO). In Japan, rituximab was approved by the Ministry of Health and Labour for the treatment of low-grade B cell lymphoma in September 2002 and for the treatment of aggressive B cell lymphoma in September 2003. The patients with B cell lymphomas were divided into two groups (the rituximab group and the non-rituximab group) based on whether they had received induction therapy containing rituximab in order to determine the benefit of rituximab as part of first remission induction therapy. This study received approval by the responsible ethics committee.

Patients

The patients included in this study were older than 15 years and were newly diagnosed as having mature B cell lymphoma with CD 20 expression by pathological or cytological examination during the period of the study. The pathological diagnosis of each institution was used. Both limited and advanced stage patients based on the Ann-Arbor classification were included (Carbone *et al*, 1971). Patients were excluded if they were human immunodeficiency virus (HIV)-positive or had central nervous system involvement at the time of presentation. All patients fitting the above criteria were serially enrolled. Final statistical analysis was performed for patients who received systemic chemotherapy, whether or not the intention was curative.

Clinical characteristics of the patients included in this survey

All patients' pathological diagnoses were done based on the WHO classification. Age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), lactate dehydrogenase (LDH) levels, clinical staging (Ann-Arbor classification), number of extra-nodal lesions (0, 1 vs. ≥2) were also collected and used to calculate the International Prognostic Index (IPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993) and the revised IPI (R-IPI; Sehn *et al*, 2007). The primary remission induction therapy regimen of all enrolled patents was determined. Usage of rituximab was the focus of this investigation. The kinds of chemotherapy were divided into two groups: those containing anthracyclin and those not containing anthracyclin.

A complete response to treatment was defined as the disappearance of all clinical evidence of disease. Progression-free survival (PFS) was defined as the interval from the diagnosis to the first recurrence of disease (progression or relapse), death from any cause, or the date of the last follow-up in patients who had no relapse. Overall survival (OS) was defined as the interval from diagnosis to death from any cause. Systemic therapy was initiated promptly after diagnosis for almost all of the patients (usually within 1 month).

Statistical analysis

The patients' clinical characteristics and treatment outcomes were compared between patient groups who received systemic chemotherapy with and without rituximab for first induction therapy. The primary endpoint of this study was to confirm the benefit of rituximab for patients with B cell lymphoma when used in remission induction by evaluating the 2-year PFS and

2-year OS. PFS and OS were assessed using the Kaplan–Meier method, and the groups were compared using the log-rank test. A multivariate Cox regression analysis was performed to assess the effects of treatment and the various baseline prognostic factors on PFS and OS. The heterogeneity of treatment effect on the survival outcomes was also examined across the different risk groups based on the R-IPI. The patients with B cell lymphoma were analysed according to pathological diagnosis; therefore, the variables for patients with DLBCL and those with FL were also assessed separately. The analysis is based on follow-up until January 2007. The prognostic variables were compared between the groups using the Mann–Whitney *U*-test for continuous variables and the chi-squared test for categorical variables. All *P* values are two-tailed. Statistical analysis was performed using STATA 8.1 (StataCorp. LP, College Station, TX, USA) and Review Manager (REVMAN; version 5.0. Copenhagen Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). *P* values < 0·05 were considered significant.

Results

All B cell lymphoma patients

A total of 1229 patients with newly diagnosed mature B cell lymphoma were enrolled in the study. Of these, 1126 patients (91·6%) received systemic chemotherapies. Patients given rituximab alone for induction were also included. Patients who received systemic therapies were the subject of this analysis, so that patients given radiation alone or eradication of *Helicobacter pylori* alone for induction were excluded. The pathological classifications are listed in Table I. The breakdown of the pathological classification was significantly different between the groups with and without rituximab for induction therapy (Table I). The ratio of patients with FL was higher in the rituximab group. This was caused by the different approval dates of rituximab for indolent B cell lymphoma and aggressive B cell lymphoma. Therefore, direct comparison of the clinical outcomes between these two groups was not considered appropriate, and the analyses were performed separately for each pathological group. Overall, 762 (67·7%) of these patients were diagnosed as having DLBCL, and 215 (19·1%) were diagnosed with FL. Thus, 86·8% (977/1126) of the patients were classified as having DLBCL or FL, so that these two diseases represented the majority of mature B cell lymphoma.

Table I. Pathological subtype of patients (n = 1126).

Histology at diagnosis	Rituximab group (n = 348)	Non-rituximab group (n = 778)	Total (n = 1126) %
DLBCL	184	578	762 (67·7)
Burkitt lymphoma	1	17	18 (1·6)
Follicular lymphoma	111	104	215 (19·1)
Small lymphocytic lymphoma	1	9	10 (0·9)
Lymphoplasmacytic lymphoma	5	8	13 (1·2)
Splenic marginal zone lymhoma	0	3	3 (0·3)
MALT-lymphoma	14	20	34 (3·0)
Nodal marginal zone B cell lymphoma	9	0	9 (0·8)
Mantle cell lymphoma	18	26	44 (3·9)
Others	5	13	18 (0·7)

DLBCL, diffuse large B-cell lymphoma; MALT-lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

DLBCL

A total of 762 DLBCL patients were enrolled. Of these, 184 patients received rituximab as part of the first-line treatment in combination with chemotherapy (rituximab group), and 578 patients were treated by chemotherapy alone (non-rituximab group). This difference in patient number was caused by the date of rituximab approval (September 2003 for aggressive B cell lymphoma) and the time period of the study (from January 2000 to December 2004). After approval, almost all DLBCL patients were treated with rituximab, but rituximab was available for only 1 year and 4 months of the 5-year study period. The patients' characteristics are listed in Table II. The ratio of cases receiving anthracyclin containing regimens in each group was not significantly different (rituximab group, 183/184; non-rituximab group, 560/578; P = 0·057). The prognostic variables (IPI and IPI subgroup) were not different between the rituximab group and the non-rituximab group (Table II). The median follow-up time for living patients was 22 months for the non-rituximab group (range, 1–50 months) and 22 months for the rituximab group (range, 1–84 months). PFS was markedly improved in the rituximab group compared with the non-rituximab group [hazard ratio (HR), 0·58; 95% confidence interval (CI), 0·44–0·77; P < 0·001, Fig 1]. The 2-year estimated PFS was 64·4% (95% CI, 56·41–71·3%) in the rituximab group and 48·7% (95% CI, 44·4–52·9%) in the non-rituximab group. OS was also improved in the rituximab group compared with the non-rituximab group (HR, 0·52; 95% CI, 0·37–0·73; P < 0·001, Fig 1). The 2-year estimated OS was 78·0% (95% CI, 70·5–83·7%) in the rituximab group and 61·7% (95% CI, 57·42–65·7%) in the non-rituximab group. Looking only at the patients who received an anthracyclin-containing regimen (CHOP or a CHOP-like regimen), the PFS and OS were compared between the rituximab group and the non-rituximab group in each R-IPI risk group. R-IPI is the revised prognostic model for DLBCL in patients receiving R-CHOP; it identifies three distinct prognostic groups (very good, good and poor). Among DLBCL patients receiving an anthracyclin-containing regimen, the ratio of these risk groups in the rituximab group and the non-rituximab group was not significantly different (Table II). For the R-IPI very good risk

Table II. Characteristics of DLBCL patients (n = 762).

Characteristic	Rituximab group (n = 184)	Non-rituximab group (n = 578)	P
Age (years), median (range)	67 (20–96)	68 (16–95)	0·947*
Gender male/female	100/84	300/278	0·563†
PS at diagnosis			
0	58	182	0·309*
1	74	195	
2	26	100	
3	22	75	
4	4	26	
LDH > normal	101	346	0·233†
Extranodal site > 1	42	130	0·925†
Clinical stage			
I	30	92	0·797*
II	60	176	
III	32	118	
IV	62	192	
IPI			
L	66	174	0·141*
LI	41	138	
HI	37	115	
H	40	151	
Receiving anthracyclin-containing regimen	183	560	0·057†
R-IPI			
Very good	26	60	0·251*
Good	80	244	
Poor	77	256	

PS, ECOG performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index (L, low; LI, low-intermediate; HI, high-intermediate; H, high); R-IPI, Revised International Prognostic Index.
*Mann–Whitney U-test.
†Chi-squared test.

group, the PFS and OS of the rituximab group were not statistically different from those of the non-rituximab group (HR, 1·38; 95% CI, 0·40–4·72; P = 0·61, HR, 1·89; 95% CI, 0·42–8·49; P = 0·40 respectively) (Fig 2). However, for the R-IPI higher risk groups (good and poor), PFS was significantly improved by the addition of rituximab (HR, 0·58; 95% CI, 0·35–0·96; P = 0·035, HR, 0·54; 95% CI, 0·38–0·76; P < 0·001 respectively) (Figs 3 and 4). OS was also improved in the R-IPI poor risk group (HR, 0·48; 95% CI, 0·32–0·72; P < 0·001), and an improvement in the R-IPI good risk group was also noted, but it was not statistically significant (HR, 0·52; 95% CI, 0·26–1·05; P = 0·069). We also performed a forest plot to explore the heterogeneity between these subgroups. There was no evidence of substantial heterogeneity in the relative treatment effect on PFS and OS between different risk groups based on the R-IPI (The P value for heterogeneity was 0·35 and 0·23 respectively) (Fig 5). These results suggest that rituximab improved the clinical outcome of all DLBCL patients.

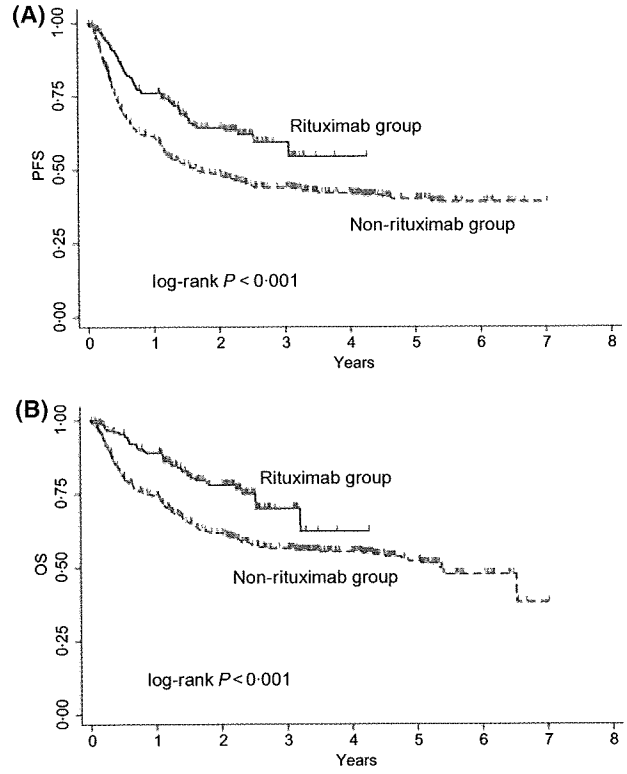

Fig 1. Progression-free survival (A) and overall survival (B) of 762 DLBCL patients. The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

Follicular lymphoma

A total of 215 FL patients were enrolled. Of these, 111 patients were in the rituximab group, and the other 104 were in the non-rituximab group. The patient number in each group was almost equal because of the date of rituximab approval (September 2002 for indolent B cell lymphoma) and the time period of the study (from January 2000 to December 2004). After approval, almost all FL cases were treated with rituximab, so that rituximab was available for 2 years and 4 months of the 5-year study period. The patients' characteristics are listed in Table III. The ratio of cases receiving an anthracyclin-containing regimen in each group was not significantly different (rituximab group, 104/111; non-rituximab group, 91/104; P = 0·159). Only three (age, LDH level, Ann-Arbor clinical stage) of the five prognostic variables that make up the FLIPI could be evaluated. These variables were not different between the rituximab group and the non-rituximab group (Table III). The median follow-up time for living patients was 37 months for the non-rituximab group (range, 1–72 month) and 41 months for the rituximab group (range, 1–80 months). PFS was markedly improved in the rituximab group compared with the non-rituximab group (HR, 0·45; 95% CI, 0·30–0·69; P < 0·001, Fig 6). The 2-year estimated PFS was 77·6% (95% CI, 68·1–84·5%) in the rituximab group and 56·3% (95% CI,

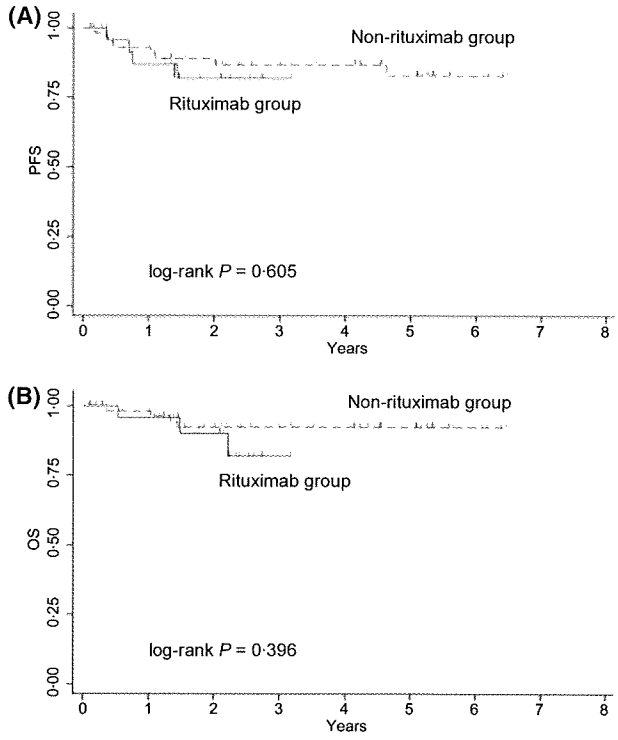

Fig 2. Progression-free survival (A) and overall survival (B) of 86 DLBCL patients (R-IPI very good risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

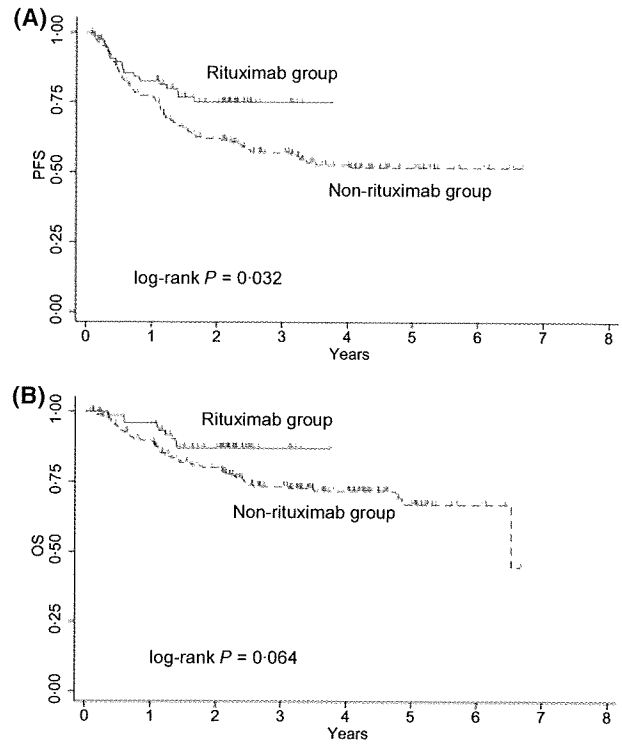

Fig 3. Progression-free survival (A) and overall survival (B) of 324 DLBCL patients (R-IPI good risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

45·9–65·5%) in the non-rituximab group. OS was also improved in the rituximab group compared with the non-rituximab group (HR, 0·35; 95% CI, 0·17–0·72; $P = 0·003$, Fig 5). The 2-year estimated OS was 94·3% (95% CI, 87·8–97·4%) in the rituximab group and 81·7% (95% CI, 72·5–88·0%) in the non-rituximab group.

A multivariate analysis was performed to assess the effect of rituximab on clinical outcome after controlling for prognostic variables. After controlling for the prognostic variables included in R-IPI and IPI itself, rituximab remained an independent prognostic predictor of both PFS (risk ratio, 0·56; 95% CI, 0·43–0·74; $P < 0·001$) and OS (risk ratio, 0·50; 95% CI, 0·36–0·70; $P < 0·001$) in DLBCL. In FL, rituximab was also an independent prognostic predictor of both PFS (risk ratio, 0·49; 95% CI, 0·32–0·74; $P = 0·001$) and OS (risk ratio, 0·44; 95% CI, 0·21–0·92; $P = 0·028$) after adjustment for prognostic variables (age, LDH level and clinical stage).

Discussion

This retrospective survey showed that the addition of rituximab significantly improved PFS and OS in patients with FL and DLBCL when used as part of first remission induction therapy. This survey was carried out among 20 hospitals belonging to CHG–NHO. The clinical data of all patients diagnosed with NHL during this study were accumulated, and the PFS and OS of B cell lymphoma patients receiving systemic chemotherapies with and without rituximab were analysed. Rituximab was approved in September 2002 for indolent B cell lymphoma and in September 2003 for aggressive B cell lymphoma in Japan. The period of this survey was from January 2000 to December 2004 (5 years); therefore, differences in clinical outcomes could be compared between the rituximab group and the non-rituximab group. NHL patients were enrolled without regard to the chemotherapeutic regimen. During the study period, 1229 mature B cell lymphoma patients were newly diagnosed, and 1126 (92%) received systemic chemotherapy. Of the 1126 patients, 977 were diagnosed with DLBCL or FL, so that these cases accounted for 86·8% of the 1126 cases of mature B cell lymphoma receiving systemic chemotherapy. Thus, the clinical outcomes of these subjects reflect those of almost the entire mature B cell lymphoma population in clinical practice.

So far, many clinical studies have shown the benefits of rituximab in the treatment of B cell lymphoma. In 1999, a single arm phase II study of a combination of rituximab and CHOP for untreated indolent B cell lymphoma was reported (Czuczman *et al*, 1999). The response rate was 95% (38 of 40), and long-term remissions were observed (Czuczman *et al*, 2004). Several randomized phase III studies have demonstrated

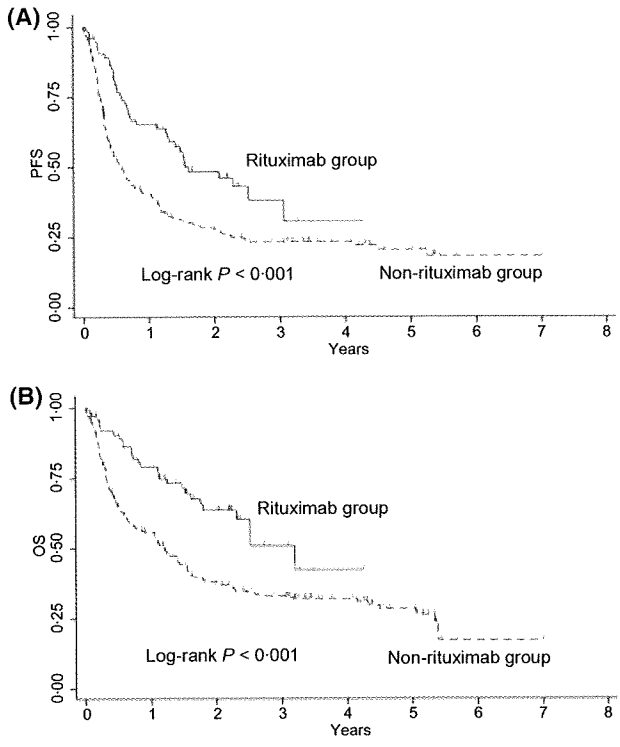

Fig 4. Progression-free survival (A) and overall survival (B) of 333 DLBCL patients (R-IPI poor risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

the advantages of the addition of rituximab to chemotherapy, both in previously untreated patients, as well as in relapsed/refractory indolent B cell lymphoma patients (Forstpointner *et al*, 2004; Hiddemann *et al*, 2005; Lenz *et al*, 2005; Marcus *et al*, 2005; Rivas-Vera *et al*, 2005; van Oers *et al*, 2006; Herold *et al*, 2007; Schulz *et al*, 2007). The German Low-Grade Lymphoma Study Group (GLSG) conducted a phase III study comparing CHOP combined with rituximab to CHOP alone, and they showed significant improvements in remission rates, PFS and OS in the combination group (Hiddemann *et al*, 2005). Other studies also showed that chemotherapy with rituximab provided a better PFS than chemotherapy alone. Recently, the Cochrane Hematological Malignancies Group performed a comprehensive systematic review and meta-analysis to compare the efficacy of chemotherapy with rituximab to the identical chemotherapy alone in patients with indolent B cell lymphoma or mantle cell lymphoma (Schulz *et al*, 2007). This analysis included seven well-controlled, randomized studies comparing rituximab–chemotherapy combination therapy with chemotherapy alone, and indicated that the rituximab–chemotherapy combination provided superior OS to chemotherapy alone.

For DLBCL, many phase III studies have proven the benefits of the addition of rituximab to chemotherapy. The Groupe d'Etude des Lymphomes de l'Adulte study showed superiority of CHOP and rituximab to CHOP alone in elderly, advanced, previously untreated, DLBCL patients with respect to PFS and OS (Coiffier *et al*, 2002). The advantage of rituximab in

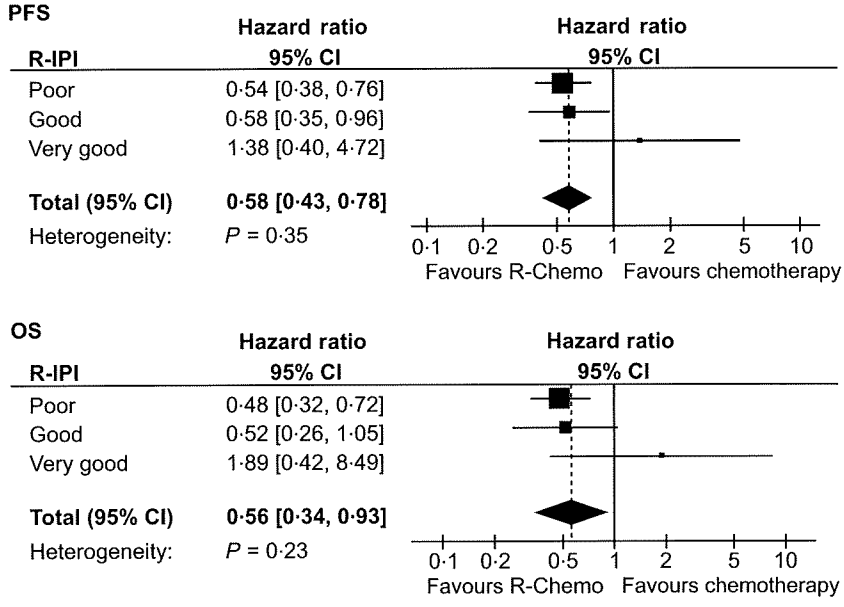

Fig 5. Disease control for DLBCL in each R-IPI risk group receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone. Disease control is shown as the hazard ratio (HR) for a disease event (progression or death). Solid squares represent risk estimates for the each R-IPI risk group. The size of squares represents the weight assigned to each R-IPI risk group and is proportional to inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals (CIs). The diamond indicates the 95% CIs for the overall HR. Values less than 1·0 indicate HRs that favour R-chemo.

Table III. Characteristics of follicular lymphoma patients (n = 215).

Characteristics	Rituximab group (n = 111)	Non-rituximab group (n = 104)	P
Age (years), median (range)	56 (26–83)	57 (23–91)	0·497*
Gender male/female	49/62	48/56	0·767†
PS at diagnosis			
0	60	53	0·395*
1	38	31	
2	8	13	
3	4	6	
4	1	1	
LDH > normal	42	47	0·274†
Clinical stage			
I	4	7	0·065*
II	28	15	
III	41	32	
IV	38	50	
Receiving anthracyclin-containing regimen	104	91	0·159†

PS, ECOG performance status; LDH, lactate dehydrogenase.
*Mann–Whitney U-test.
†Chi-squared test.

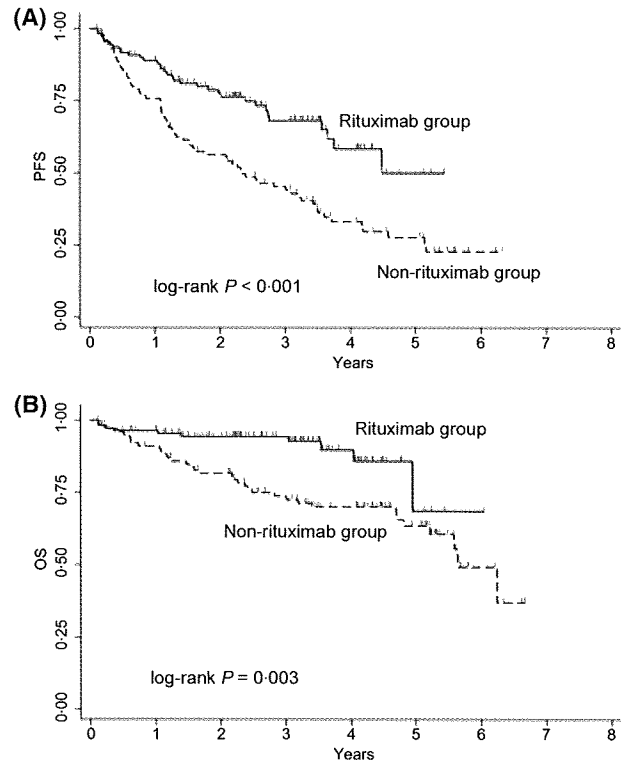

Fig 6. Progression-free survival (A) and overall survival (B) of 215 follicular lymphoma patients. The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

combination with a CHOP-like regimen for the younger DLBCL population was indicated by the intergroup cooperative study (MInT study) (Pfreundschuh *et al*, 2006). Therefore, the clinical merits of the use of rituximab in the induction treatment of mature B cell lymphoma have now been established by these well controlled, phase III studies, but the actual benefits of rituximab benefits in clinical practice have not been addressed. Prospective clinical trials for treatment have critical inclusion and exclusion criteria, and patients with poor PS or organ dysfunction are usually excluded. One population-based retrospective analysis, by the British Columbia Cancer Registry, assessed the effect of rituximab in combination with CHOP for DLBCL and demonstrated improvement in treatment outcome in clinical practice (Sehn *et al*, 2005). However, this study was limited to patients who were treated with curative intent. The present study serially enrolled all patients with mature B cell lymphoma who were newly diagnosed, and all patients receiving systemic chemotherapy, whether or not the intent was curative, were included in the analysis to evaluate the effect of rituximab. This approach reflects the actual state of management of mature B cell lymphoma patients in clinical practice.

In DLBCL, PFS and OS were better in the rituximab group than in the non-rituximab group. When DLBCL was classified by R-IPI, the benefit of rituximab was statistically identified in the good and poor risk group but not in the very good risk group. The favourable effect of rituximab seemed to be restricted in higher risk patients, but the significant heterogeneity between these subgroups was not identified by the forest plot (Fig 5). This finding might be a result of small patient numbers in the very good risk group. To clarify whether rituximab contributes to the clinical outcomes of the very good risk group or not, more cases need to be analysed.

In conclusion, this retrospective analysis showed that the use of rituximab for remission induction therapy significantly improved OS and PFS in patients with FL or DLBCL, who constitute the majority of mature B cell lymphoma patients. This study was planned to elucidate the state of NHL management in clinical practice and found that rituximab appeared to dramatically improve clinical outcomes in patients with mature B cell lymphoma.

Acknowledgements

This work was supported by Grant-in-Aid for Clinical Research from the National Hospital Organization. We thank Dr Y Hirata (NHO Hokkaido Cardiovascular Centre), Dr S Kimura (NHO Nishi Sapporo National Hospital), Dr T Komeno (NHO Mito Medical Centre), Dr Y Kitano (NHO Matsumoto Medical Centre), N Yoshio (NHO Kanazawa Medical Centre), H Inoue (NHO Fukui National Hospital), Dr A Shimazaki (NHO Himeji Medical Centre), T Soma (NHO Minami-Okayama Medical Centre), Y Takimoto (NHO Hiroshima-Nshi Medical Centre), and S Yoshida (NHO Nagasaki

Medical Centre) for the registration of patients; Dr Terasawa (Tufts-New England Medical Centre) for helpful comments.

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VOLUME 27 · NUMBER 11 · APRIL 10 2009

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography for Interim Response Assessment of Advanced-Stage Hodgkin's Lymphoma and Diffuse Large B-Cell Lymphoma: A Systematic Review

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Submitted January 7, 2008; accepted December 18, 2008; published online ahead of print at www.jco.org on March 9, 2009.

Supported by Banyu Life Science Foundation International (H19) and the Ministry of Health, Labor, and Welfare, Japan (15-2).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2711-1906/$20.00

DOI: 10.1200/JCO.2008.16.0861

ABSTRACT

Purpose
To systematically review the prognostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) for interim response assessment of patients with untreated advanced-stage Hodgkin's lymphoma (HL) or diffuse large B-cell lymphoma (DLBCL).

Methods
MEDLINE, EMBASE, SCOPUS, and Biologic Abstracts were searched for relevant studies. Two assessors independently reviewed studies for inclusion and extracted data. Relevant unpublished data were requested from the investigators if unavailable from publications. A meta-analysis of the prognostic accuracy was performed.

Results
Thirteen studies involving 360 advanced-stage HL patients and 311 DLBCL patients met our inclusion criteria. Advanced-stage HL studies included few unfavorable-risk patients. DLBCL studies were heterogeneous. FDG-PET had an overall sensitivity of 0.81 (95% CI, 0.72 to 0.89) and a specificity of 0.97 (95% CI, 0.94 to 0.99) for advanced-stage HL, and a sensitivity of 0.78 (95% CI, 0.64 to 0.87) and a specificity of 0.87 (95% CI, 0.75 to 0.93) for DLBCL. Meta-regression and subgroup analyses did not identify factors that affect prognostic accuracy.

Conclusion
For low- to intermediate-risk advanced-stage HL, FDG-PET performed after a few cycles of standard chemotherapy seems to be a reliable prognostic test to identify poor responders, warranting prospective studies to assess PET-based treatment strategies. For DLBCL, no reliable conclusions can be drawn due to heterogeneity. Interim PET remains an unproven test for routine clinical practice. Its use should be reserved for research settings where treatment regimens and imaging conditions are standardized.

J Clin Oncol 27:1906-1914. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Malignant lymphoma is the fifth most commonly diagnosed cancer in the United States.[1] With advances in treatments, Hodgkin's lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) are potentially curable lymphomas.[2,3] However, challenges remain especially in the treatment for high-risk patients,[4,5] since more than half of these patients do not achieve long-term survival with currently available standard first-line chemotherapy. A possible treatment involves intensive and toxic polychemotherapy for advanced-stage HL[6] or first-line high-dose chemotherapy with stem-cell support for DLBCL,[7] depending on individual risk of treatment failure. Therefore, better identification of poor responders to first-line therapy is important to advance risk-adapted treatment strategies.

Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a functional imaging test that has become widely used in the management of both HL and non-Hodgkin's lymphoma (NHL).[8] Studies that assessed FDG-PET as a prognostic tool performed during chemotherapy have reported the ability to predict poor outcomes.[8] However, the studies used different design, conduct, and reporting, making interpretation of the results difficult. In particular, inclusion of heterogeneous populations with different categories of disease (eg, limited-stage *v* advanced-stage HL or DLBCL

Table 1. Studies of PET for Interim Response Assessment of Malignant Lymphoma Included in the Systematic Review

Study	Year	Country	Study Design	No. of Involved Institutions	Start of Follow-Up Period	Follow-Up (months)		Pretherapy Scan to Confirm FDG Avidity (%)
						Median	Range	
Advanced-stage HL + DLBCL								
Kostakoglu et al[32]	2006	USA	Retrospective	1	Start of therapy	21†	3-47	100
Advanced-stage HL								
Friedberg et al[33]	2004	USA	Prospective	3	Pre-therapy PET	24†	10-32	100
Hutchings et al[37]	2005	UK	Retrospective	1	Diagnosis of lymphoma	40†	6-125	100
Gallamini et al[30]	2006	Italy	Prospective	11	Diagnosis of lymphoma	20‖	2-46	100
Hutchings et al[13]	2006	Denmark	Prospective	3	Diagnosis of lymphoma	22	6-40	100
Zinzani et al[14]	2006	Italy	Prospective	1	NR	18	12-27	100
Gallamini et al[29]	2007	Italy + Denmark	Prospective	14	Diagnosis of lymphoma	26†	4-62	100
DLBCL								
Spaepen et al[34]	2002	Belgium	Prospective	1	End of therapy	36††	19-51	97†
Haioun et al[31]	2005	France	Prospective	4	Study enrollment	24†	NR	100
Mikhaeel et al[12]	2005	UK	Retrospective	1	Diagnosis of lymphoma	24†	NR	100
Fruchart et al[35]	2006	France	Prospective	1	Start of therapy	19	2-35	100
Querellou et al[38]	2006	France	Retrospective	1	Start of therapy	15†¶	9-28	100
Ng et al[36]	2007	Australia	Retrospective	1	Start of therapy	28	2-81	Partial

(continued on following page)

ν other aggressive NHLs) clearly affects the clinical applicability of the study results because each category has different clinical profiles (eg, treatment strategies, response, and prognosis). In this systematic review, we assessed the prognostic accuracy of FDG-PET performed during first-line therapy to predict disease progression or relapse in patients with advanced-stage HL and DLBCL, paying particular attention to the clinical applicability of the reported results.

METHODS

Data Sources and Searches

We searched Ovid MEDLINE and EMBASE from 1966 through July 2006,[9] and PubMed from August 2006 through July 2007 without language restriction. The search strategy can be found in online-only Appendix Table A1. This search was augmented by searches of SCOPUS and Biologic Abstracts. We also examined the reference lists of eligible studies, review articles, and textbooks.

Study Selection

Two reviewers (T.T., H.N.) screened abstracts and determined eligibility. Full-text articles were reviewed when abstracts did not provide sufficient information for determination. We included studies that evaluated FDG-PET performed between the first and the fourth cycle of first-line chemotherapy for patients with advanced-stage HL or DLBCL. We included both prospective and retrospective studies, and we considered clinical follow-up with or without pathologic confirmation to be a reference standard. We included studies that evaluated at least 10 patients and included at least five patients who progressed during chemotherapy or relapsed through clinical follow-up. We accepted studies in which patients received high-dose chemotherapy followed by autologous stem cell transplantation as long as it was administered as a part of primary therapy or consolidation therapy after standard induction chemotherapy. We excluded abstracts, editorials, comments, letters, and review articles. We excluded studies that enrolled patients with HIV-associated or post-transplant lymphoproliferative disorders.

Many studies did not meet all the inclusion criteria, but did partially include a relevant patient population. For these studies, we contacted the authors for relevant individual patient or subgroup data. When there was no response after 4 weeks, another correspondence was sent. When there was no response after the third communication attempt, we considered the request rejected.

Data Extraction and Quality Assessment

Two independent, board-certified hematologists (T.T., H.N.) abstracted relevant data. We extracted patients' demographic and clinical characteristics including the International Prognostic Scores (IPS) for advanced-stage HL[4] or the International Prognostic Indexes (IPI) for DLBCL,[5] therapeutic interventions, interim PET results, and final clinical outcomes. We subdivided the treatment failures into three categories based on the relative timing to the completion of first-line therapy: during therapy, after 1 year from diagnosis or the start of therapy, and in between. When the timing of completion of first-line therapy was unclear, we arbitrarily considered the treatment period to be 6 months. We also extracted the number of cases in remission but censored from follow-up within 1 year from the start of therapy (early censoring). One nuclear medicine specialist (T.N.) evaluated the technical specification and quality of PET procedures using recommended guidelines.[10] Reviewers were not blinded to the name of the journal. Inconsistencies between reviewers were either clarified by the authors or resolved by consensus.

To evaluate the quality, applicability, and reporting of the studies, we used QUADAS, a recently proposed tool to assess the quality of studies of diagnostic accuracy included in a systematic review.[11] Details on how we scored each item can be found in online-only Appendix Table A2. We assessed only published data and did not use unpublished data because the latter was not available from all the studies.

Data Synthesis and Statistical Analysis

For each study, we constructed a 2×2 contingency table consisting of true positive (TP), false positive (FP), false negative (FN), and true negative (TN), where all patients were categorized according to whether they were PET positive or negative, and whether they experienced treatment failure. In the main analysis, we employed the entire clinical follow-up as the reference standard. In sensitivity analysis, we categorized patients using shorter clinical follow-up as the alternative reference standard to focus on very early treatment failures (only during therapy or < 6 months), or early treatment failures (< 12 months). We counted patients in remission during the specified follow-up period as no treatment failure even if they eventually experienced treatment failure thereafter. We counted early censorings as no treatment failure in the main analysis. In sensitivity analysis to explore a worst-case scenario, early censorings were excluded from the analysis, and then counted as FP if they had negative PET results and were lost to follow-up early without treatment

Table 1. Studies of PET for Interim Response Assessment of Malignant Lymphoma Included in the Systematic Review (continued)

Study	No. of Chemotherapy Cycles Before PET Scan	Duration Between Chemotherapy and PET Scan (days)	No. of Total Participants*	Women		Age (years)	
				No.	%	Median	Range
Advanced-stage HL + DLBCL							
Kostakoglu et al[32]	1	8-15 for HL, 15-22‡ for DLBCL	34§	23†	49	48.2†‖	18-76
Advanced-stage HL							
Friedberg et al[33]	3¶	NR	22	NR†	36	NR†	18-60
Hutchings et al[37]	2 or 3	8-15	28	42†	49	36.7†	15-73
Gallamini et al[30]	2	11.6‖	108	57	53	32.6‖	14-79
Hutchings et al[13]	2	8-15	46	28†	36	36	18-74
Zinzani et al[14]	2	NR	40	21	53	32	14-48
Gallamini et al[29]	2	NR	106#	127†	49	32†	14-79
DLBCL							
Spaepen et al[34]	3 or 4#	14†† or 21‡	47	18†	26	40†	3-78
Haioun et al[31]	2	13-14†† or 20-21‡	83	34†	38	53†	17-78
Mikhaeel et al[12]	2 or 3	NR	57	56†	46	55†	20-84
Fruchart et al[35]	2 or 3	12†† or 18‡	35	13†	33	56†	24-77
Querellou et al[38]	2, 3, or 4¶‡‡	15-21‡	21	NR†	33	NR†	17-75
Ng et al[36]	2, 3, or 4§§	12-14†† or 19-21‡	44	21	48	60	27-83

Abbreviations: FDG, fluorodeoxyglucose; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NR, not reported; PET, positron emission tomography; R, rituximab.
*Only advanced-stage HL or DLBCL patients were included in this systematic review.
†Data abstracted from total participants of original report, not exclusively for relevant patient population.
‡For tri-weekly cycle chemotherapy [eg, (R-)CHOP].
§Including 10 advanced-stage HL patients and 24 DLBCL patients.
‖Mean.
¶Patients underwent PET at the midpoint of the whole chemotherapy cycles (the end of the second cycle for 4-cycle chemotherapy regimens, the third cycle for 6-cycle regimens, and the fourth cycle for 8-cycle regimens).
#Only patients not included in the previous reports[13,30] were left.
**Only patients in long-term remission.
††For bi-weekly cycle chemotherapy [eg, (R-)ACVBP].
‡‡Eleven patients underwent PET at the end of the fourth cycle.
§§Eleven patients underwent PET at the end of the fourth cycle.

failure. Three studies reported intermediate PET results as minimal residual uptake (MRU).[12–14] We considered this category negative scan in the main analysis because this was how investigators analyzed the results. In sensitivity analyses, MRU results were excluded from analysis, considered positive, considered positive in the case of treatment failure and negative in the case of continuing remission (best-case scenario), and considered negative in the case of treatment failure and positive in the case of continuing remission (worst-case scenario).

We calculated sensitivity, specificity, and likelihood ratios (LRs) for each study. For the estimation of 95% CI, we used the binominal Wilson method for sensitivity and specificity, and normal approximation for LRs. Then we combined summary statistics, 95% confidence regions of summary sensitivity and specificity, and summary receiver operating characteristic (ROC) curves by the hierarchical SROC method,[15] which takes into account both within-study and between-studies variation. We fitted the model by using maximum likelihood estimation implemented in the GLLAMM algorithm[16] in STATA (version 9.2; Stata Corp, College Station, TX), and depicted the summary ROC curves and confidence regions for summary sensitivity and specificity.[17] We estimated the Q* statistic,[15] the point on the curve where sensitivity equals specificity, as global measures for the summary ROC.

To explore heterogeneity, we performed subgroup analyses by visual assessment of ROC plots and univariate meta-regression analyses. In the meta-regression, we incorporated study design or clinical characteristics as covariates into the bivariate model using Meta-Analyst (Tufts Medical Center, Boston, MA). Our preplanned analyses included characteristics of study design (prospective *v* retrospective), whether studies included more than 10 patients with treatment failure, rates of treatment failure, adoption of combined FDG-PET and computed tomography (FDG-PET/CT), the mean number of chemotherapy cycles before PET, timing of PET scan after the administration of chemotherapy, percentage of high or high-intermediate risk for DLBCL, and percentage of rituximab (R) use for DLBCL. We also performed posthoc analyses on the use of high-dose chemotherapy. Two-sided *P* values lower than .05 were considered to be statistically significant.

RESULTS

Search Results

Online-only Appendix Figure A1 summarizes the search results. We retrieved 23 full reports for further review and contacted nine authors for additional data. We excluded three studies that presented the same participants as previous reports,[18–20] three studies that did not provide information to calculate prognostic accuracy,[21–23] two studies that adopted nondedicated PET scanner,[24,25] one study with fewer than 10 relevant participants,[26] one study with fewer than five patients who progressed or relapsed,[27] and one study that evaluated patients during salvage therapy.[28] One study[29] presented updated results combining previous reports from two independent groups[13,30] together with 106 newly evaluated patients from both groups. In this report, we included only the added subpopulation as an independent study. Three studies reported FDG-PET results at completion of second cycle and fourth cycle of chemotherapy.[13,14,31] We abstracted data only on the second cycle in these studies. One study evaluated

