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13) 朝長万左男：造血器腫瘍化学療法ガイドライン作成に当たっての問題点、第３回日本臨床腫瘍学会総会、平成１７年３月４日～５日（横浜）

H．知的財産権の出願・登録状況

なし。

厚生労働科学研究費補助金 総括・分担研究報告書
【研究分野名】平成16年度 疾病・障害対策研究分野
【研究事業名】がん臨床研究
【研究課題名】難治性悪性リンパ腫の治療に関する研究
【報告書区分】分担
【文献番号】200400507A

分担研究者:上田龍三　名古屋市立大学大学院医学研究科教授

難治性悪性リンパ腫に対する分子標的治療薬を用いた薬物療法の研究(臨床試験の実施)

研究要旨

（1）未治療進行性低悪性度リンパ腫における Rituximab + standard CHOP と Rituximab + bi-weekly CHOP とのランダム化比較試験（JCOG0 203-MF）にこれまでに３症例登録し、多施設共同研究を実施するとともに、（2）もう一つの難治性悪性リンパ腫であるT/NK 細胞性リンパ腫に対する抗 CCR4 抗体療法の確立を目指した基礎的検討としてこれらのリンパ腫細胞における CCR4 発現の頻度およびその臨床的意義についての検討を行った。

(1) 本研究班全体で取り組む JCOG0203-MF「未治療進行期低悪性度 B 細胞リンパ腫に対する抗CD20 抗体療法+化学療法[Rituximab+standard CHOP(R・CHOP) vs Rituximab+bi-weekly CHOP(R・bi-CHOP)]のランダマイズ化比較臨床第 II/III 相試験」:施設内 IRB および倫理委員会の承認が平成14年11月21日に得られた。その後リツキシマブの6回投与への変更に関しての施設内 IRB の承認を平成16年2月13日に得た。これまでに参加同意取得後に適格症例3例の登録を行い全治療を完了した。

(2)

A. **研究目的:**我々はキメラ型およびヒト化抗 CCR4 抗体療法の開発のための基礎的研究として、昨年度報告した成人T細胞性白血病・リンパ腫(adult T-cell leukemia/lymphoma: ATLL)におけるケモカイン受容体 CCR4 の発現の意義に加えて、もう一つの難治性悪性リンパ腫であるT/NK 細胞性リンパ腫におけるケモカイン受容体である CCR4 の発現とその臨床

的意義についての検討を行った。

B. **研究方法:**ケモカイン受容体である CXCR3 および CCR4 の発現を 1C6 抗体および KM2160 抗体を用いた免疫染色で検討した。各種臨床パラメーターと生存期間に関して統計学的に解析した。

C. **研究結果:**WHO 分類における前駆T細胞性リンパ芽球性リンパ腫、ALK 陽性未分化大細胞型リンパ腫、節外性 NK/T 細胞性リンパ腫においては CCR4 と CXCR3 の発現はともに全く認められなかった。CXCR3 の特徴的な発現は、血管免疫芽球性T細胞性リンパ腫(AILT)において認められた。それに対して、CCR4 の発現は ALK 陰性未分化大細胞型リンパ腫や菌状息肉症の転化期において高頻度に認められた。また末梢性T細胞性リンパ腫では最も頻度の高い Peripheral T-cell lymphoma, unspecified (PTCLU)においては CXCR3(18 例)と CCR4(19 例)の発現例がともに認められケモカイン受容体の発現から見ても PTCLU は異なった疾患群を含んでいる事が示唆された。そこで PTCLU 50 例において CCR4 発現の臨床的意義について検討を進めた。Cox 比例ハザードモデルを用いた多変量解析の結果 CCR4 発現はB症状、LDH 上昇、貧血の存在とともに有意な予後不良因子であることが明らかになった。また興味深いことに免疫抑制性T細胞(Immunoregulatory T-cell: Treg)のマーカーである FoxP3 の発現と CCR4 の発現には正の相関を認め、PTCLU の中で CCR4 陽性のリンパ腫は免疫抑制性T細胞に由来しておりそのために強い免疫抑制状態にあることが予後不良となっている原因である可能性が示唆された。

D. **考察:** ATLL のみならず CCR4 陽性 PTCLU も抗 CCR4 抗体の治療応用が可能であることが示された。

E. **結論:**JCOG0203-MF において低悪性度B細胞性リンパ腫に対するリツキサンと化学療法の至的併用療法を確立することは重要な課題であり、研究意義を詳しく説明し御理解を得た上での本研究への参加症例のスムーズな蓄積努力が必要である。またT細胞性難治性リンパ腫に属する末梢性T細胞性リンパ腫に対してもリツキサン同様の抗体療法を開発してゆく努力が必要である。

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厚生労働科学研究費補助金　総括・分担研究報告書

【研究分野名】平成16年度 疾病・障害対策研究分野

【研究事業名】がん臨床研究

【研究課題名】難治性悪性リンパ腫の治療に関する研究

【報告書区分】分担

【文献番号】200400507A

分担研究者　鈴木孝世　滋賀県立成人病センター　第2内科主任部長

分担研究項目　難治性悪性リンパ腫の治療に関する研究(臨床試験の実施)

研究要旨

我々が施行してきた、再発・再燃 B 細胞リンパ腫症例に対するキメラ型抗 CD20 抗体リツキシマブの多施設共同による臨床第 I 相試験および臨床第 II 相試験の結果、[再発・再燃低悪性度 B 細胞リンパ腫に対する奏効率 61% (37/61); 95%信頼区間 47-73%] に基づいて、リツキシマブが 2001 年 9 月に厚生労働省に承認され、本邦において保険診療下での使用が可能になった。

平成 13 年度当初より、本臨床試験（未治療進行期低悪性度 B 細胞リンパ腫に対するリツキシマブと CHOP 療法併用のランダム化臨床第 II/III 相試験）のプロトコールの立案・作成作業を行ない、フルプロトコールが JCOG 臨床試験審査委員会による承認が得られた。 これを受け、滋賀県立成人病センター倫理委員会（IRB）においても、リツキシマブと CHOP 療法併用のランダム化臨床第 II/III 相試験実施の承認を得た。 途中、プロトコールの改訂(リツキシマブ4回投与→6回投与)を受け、滋賀県立成人病センターにおいても迅速審査の結果、2003年 12月1日にIRB承認となった。

当センターにおいて、本年度は 5 症例を登録し、合計 10 症例について臨床試験を施行している。

A. 研究目的

本研究の目的は、近年開発され臨床に導入された分子標的治療薬リツキシマブを用いて、

難治性悪性リンパ腫の有効な薬物療法を確立することであり、ひいては難治性悪性リンパ腫患者の生命予後と生活の質を改善させることを目指す。

未治療進行期CD20陽性・低悪性度B細胞リンパ腫患者を対象として、マウス／ヒトキメラ型抗CD20抗体リツキシマブ と CHOP 療法の併用療法を対照群 (R・CHOP)とし、化学療法の用量強度増強および顆粒球コロニー刺激因子(granulocyte colony-stimulating factor; G-CSF)併用による抗体療法の効果増強が期待される biweekly CHOP 療法とリツキシマブの併用療法 (R・Bi-CHOP)とのランダム化比較第 II/III 相試験を行う。

第 II 相部分の primary endpoint は完全奏効割合 [complete response(CR)rate]、secondary endpointsは (1) 奏効率、(2) 無増悪生存、(3) 生存、(4) 治療の短期安全性とする。第 III 相部分の primary endpoint は無増悪生存、secondary endpoints は生存および安全性とする。第 II 相から第 III 相部分への移行の可否は、Japan Clinical Oncology Group (JCOG)データセンターによる中間解析結果に基づいて、JCOG 効果・安全性評価委員会による評価と判断に従う。

B. 研究方法(倫理面への配慮)

本研究は JCOG との共同研究として施行している。 プロトコールの作成には以下の過程を経て作業を進めて来た。

1) JCOG リンパ腫グループのプロトコール検討委員会で本臨床試験の基本方針を検討し、合意を得た。
2) プロトコールコンセプトを作成し、JCOG リンパ腫グループの全施設に送付してアンケート調査を行った上で、JCOG リンパ腫グループの班会議においてグループ全体の合意を得た。
3) JCOG臨床試験審査委員会とJCOG運営委員会にプロトコールコンセプトを提出して審査を受け承認された。
4) 21 世紀型医療開拓推進研究の応募課題として本臨床試験の研究計画書を厚生労働省に提出し、研究課題として採択された。
5) JCOG Protocol Review Committee において、他分野の臨床腫瘍医、統計学者、データマネージャーが参加して、臨床試験研究としてプロトコールの細部を検討した。
6) 2001 年 9 月 7 日にリツキシマブの本邦での発売が開始された。
7) JCOG Protocol Review Committee における検討に基づいて完成したフルプロトコールを 2002 年 3 月 4 日に JCOG 臨床試験審査委員会に提出し、承認が得られた。

8) 2002年7月31日に滋賀県立成人病センターの倫理委員会による審査・承認を経た。

9) start-up meetingに参加した後、1症例を登録し臨床試験を開始した。

10) プロトコールの改訂(リツキシマブ4回投与→6回投与)を受け、滋賀県立成人病センターにおいても迅速審査の結果、2003年12月1日にIRB承認となった。

倫理面への配慮

適切な症例選択規準と治療中止規準の設定により、被験者の安全性を最大限に確保している。また、ヘルシンキ宣言などの国際的倫理原則に従い、以下を遵守している。

1) 研究実施計画書のinstitutional review board (IRB)による審査・承認が得られた施設のみが症例を登録する。

2) 説明文書を用いて十分な説明を行い考慮の時間を設けた後、自由意志に基づく同意を患者本人より文書で得る。

3) 直接個人が識別できる情報を用いず、データベースのセキュリテイを確保し、個人情報保護を厳守する。

4) 臨床試験審査委員会、効果・安全性評価委員会、監査委員会による、臨床試験研究の第三者的監視を実施する。

C. 研究結果

滋賀県立成人病センターでは、本年度新たに5症例を登録し(合計 10 症例)、A 群(3 週間毎のCHOP 療法群)3例、B群(2週間毎の CHOP 療法群)2例に割り付けられている。治療計画に従って治療を行っているが、現在までに報告すべき有害事象はおこっていない。有効性の解析については、JCOGデータセンターにて症例集積の上施行される予定である。登録症例は下記の登録条件を満たしている。

<u>症例登録条件</u>

(1) 病理組織診断にて悪性リンパ腫と診断され、免疫組織染色もしくはflow cytometry法によりCD20陽性の低悪性度 B細胞リンパ腫と診断された症例。

(2) Ann Arbor臨床病期 : III期もしくはIV期。

(3) 年令は20歳以上、74歳以下。

(4) Eastern Cooperative Oncology Groupの performance status (PS) 0-2。

(5) 測定可能病変を有する症例。

(6) 以前に化学療法・放射線治療・インターフェロン・抗体療法を受けていない症例。

(7) 緑内障の既往のない症例。

(8) 十分な骨髄・肝・腎・心・肺機能を有する症例。

(9) リツキシマブ の第 1 回目投与時に入院可能な症例。

(10) 文書による同意が得られた症例。

治療計画

6コースの CHOP 療法は2または 3 週間毎に行い各コースでリツキシマブを計6回併用する。

リツキシマブ 375 mg/m^2 の 1 回点滴静注は各 CHOP 療法施行予定日の 2 日前 (day 1) に投与する。

CHOP 療法

薬剤	投与量 (投与法)	投与日 (day)
Cyclophosphamide (CPA)	750 mg/m^2 (DIV)	3
Doxorubicin (DOX)	50 mg/m^2 (DIV)	3
Vincristine (VCR)	1.4 mg/m^2 (IV) (Max. 2.0 mg)	3
Prednisolone (PSL)	100 mg/body (PO)	3-7

D. 考察とE. 結論

臨床試験の症例登録中のため、現在は本研究の結論を導き出せる状況ではない。しかし、進行期中高悪性度 B 細胞リンパ腫においてリツキシマブとCHOP 療法併用の有効性が CHOP 療法単独の有効性を凌駕することを示したランダム化第 III 相比較試験の成績が公表されるなど、B 細胞リンパ腫全体においてリツキシマブと CHOP 療法併用が標準治療もしくは基準治療と見なされつつある状況を考慮すると、本研究によって、進行期低悪性度 B 細胞リンパ腫においてもリツキシマブと biweekly CHOP 療法の併用がより優れていることが証明できれば、新たな標準治療確立と当該疾患患者の予後改善につながり、国際的にも高い医学的貢献が期待できる。実際、登録5症例についても良好な治療効果が得られている。

本年度は 5 症例を登録し、新たに治療を開始した。当該研究においては合計 10 症例の登録となり、施設においても安全に治療が行えるようになった。即ち、予測可能な有害事象に対して

は速やかに対処し得、重篤な有害事象は観測されなかった。B 群(2 週間に一度の R-CHOP 療法)においては治療を重ねる毎に骨髄抑制が強く現れ、全 6 コースを入院で試行しなければならない症例が多かった。入院が長期にわたる点に関して、患者様の精神的苦痛もあり、改善の余地を探る必要があると思われた。

当該研究においては、除外基準として HBsAg 陽性があげられているが、HBsAg が陰性であっても、HBsAb 陽性患者様の場合は治療による(特にステロイドホルモンによる)免疫抑制状態が HBV を活性化し、B 型肝炎の再燃を来す可能性が否定できない。実際、重症の再生不良性貧血の患者様に ATG・ステロイドを投与後、B 型肝炎の再燃をみた経験がある。よって、我々は、HBsAg、HBsAb がともに陰性患者様を試験に登録してきた。HBsAb 陽性症例については、HBV-DNA ポリメラーゼの測定も意義のあるところかもしれない。B 型肝炎はいまや国民病であることからも、今後のプロトコール研究においては十分な検討を要すると思われる。

治療成績はおおむね良好である印象を受けるが、症例数や、時期を見ての解析が待たれる。当該研究の途上、リツキシマブの 8 回投与が保険適応になったことから、登録可能症例の内、数名がリツキシマブの 8 回投与を希望することにより、登録が出来なかった。EBM に準拠した実施医療と、保健医療の整合性が強く求められるところである。

F. 健康危険情報

なし。

G. 研究発表

1. 論文発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし。

2. 実用新案登録

なし。

3. その他

なし。

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Review Article

Clinical Trials for Malignant Lymphoma in Japan

Kensei Tobinai[1] and Tomomitsu Hotta[2]

[1]Hematology Division, National Cancer Center Hospital, Tokyo and [2]Department of Hematology/Oncology, Tokai University School of Medicine, Isehara, Kanagawa, Japan

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Clinical Trials for Malignant Lymphoma in Japan

Kensei Tobinai[1] and Tomomitsu Hotta[2]

[1]Hematology Division, National Cancer Center Hospital, Tokyo and [2]Department of Hematology/Oncology, Tokai University School of Medicine, Isehara, Kanagawa, Japan

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The results of the clinical trials by the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) and those of the industry-supported trials mainly conducted by the members of JCOG-LSG are summarized. In the treatment of advanced aggressive non-Hodgkin's lymphoma (NHL), we investigated the efficacy of granulocyte colony-stimulating factor (G-CSF)-supported, dose-intensified strategies. Based on the results of a randomized phase II study (JCOG9505), we conducted a phase III study, JCOG9809, comparing CHOP and biweekly CHOP. However, JCOG9809 was terminated early based on the results of a planned interim analysis, because it was deemed highly unlikely that biweekly CHOP would be superior to standard CHOP. For aggressive ATL, a G-CSF-supported, dose-intensified, multi-agent regimen (JCOG9303; LSG15) showed superior efficacy to our historical controls. To establish a new standard for ATL, we conducted a phase III study, JCOG9801, comparing LSG15 and biweekly CHOP. To develop new agents for lymphoid malignancies, we focused on irinotecan hydrochloride, interferon-α, cladribine and oral fludarabine. Among them, cladribine and oral fludarabine are promising for indolent B-cell malignancies. The Japanese phase I and II studies of rituximab, a chimeric anti-CD20 monoclonal antibody, in relapsed indolent and aggressive B-NHL showed high efficacy with minimal toxicities, which led us to conduct combination studies with chemotherapy for B-NHL. In addition, a phase I study of a radiolabeled anti-CD20 antibody (ibritumomab tiuxetan) was completed in 2003, and a phase II study for indolent B-NHL will be initiated. The multicenter trials by the JCOG-LSG and industry-supported new agent studies will contribute to further improvement in the treatment of malignant lymphoma.

Key words: Japan Clinical Oncology Group (JCOG) – malignant lymphoma – adult T-cell leukemia-lymphoma – new agent – antibody therapy

INTRODUCTION

Most clinical trials for malignant lymphoma in Japan have been conducted in two ways: multicenter trials conducted by cooperative study groups and industry-supported trials for new agent development. In this article we review the present status of the clinical trials conducted by the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) and that of the industry-supported trials mainly conducted by the members of JCOG-LSG.

JCOG is a multicenter cooperative oncology group, supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare, Japan. JCOG has a common Data Center and the Steering Committee, consisting of a JCOG representative and chairpersons from the Clinical Trial Review Committee, Data and Safety Monitoring Committee, Audit Committee and Education and Training Committee, and each of 13 cancer study groups (1). All JCOG studies should be conducted according to the Good Clinical Practice guidelines, i.e. the study should be ethical and scientific, be approved by the institutional review board of each participating institution, and be conducted after obtaining written informed consent.

JCOG-LSG now consists of 46 institutions throughout Japan, and has conducted 21 multicenter trials, including eight randomized controlled trials for lymphoid malignancies, i.e. advanced aggressive non-Hodgkin's lymphoma (NHL) (JCOG8101, 9002, 9505, 9809), indolent B-NHL (JCOG0203), adult T-cell leukemia-lymphoma (ATL) (JCOG9801), and multiple myeloma (JCOG9301, 0112).

In this review, treatment strategies of advanced aggressive NHL, ATL and Hodgkin's lymphoma by the JCOG-LSG are

For reprints and all correspondence: Kensei Tobinai, Hematology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: ktobinai@ncc.go.jp

Table 1. Results of JCOG trials for advanced, aggressive NHL

Protocol/Regimen	Drugs	Phase	No. of patients	%CR (no.)	MST (months)	Survival (%)	Ref.
JCOG8101		III	190	57 (93/163)	21	32 (4-year)	2,3
LSG1-VEPA	VCR, CPA, PSL, DOX		95	52 (42/81)	17	27 (4-year)	
LSG2-VEPA-M	VCR, CPA, PSL, DOX, MTX		95	62 (51/82)	24	37 (4-year)	
JCOG8701	VCR, CPA, PSL, DOX, BLM, MTX, VDS, ETP, PCZ	II	338	72 (193/267)	39	48 (5-year)	4
JCOG9002	VCR, DOX, ETP, PSL, BLM, MTX, VDS, ETP, PCZ	III	447	67 (301/447)	NA	56 (5-year)	5
JCOG9505[a]	VCR, CPA, PSL, DOX	R-II	70	56 (39/70)	12	42 (4-year)	11
JCOG9506[a]	VCR, CPA, PSL, DOX, CBDCA, CPA, ETP, DEX	II	43	NA	NA	58 (3-year)	NA
JCOG9508[b]	VCR, CPA, PSL, DOX	II	213	NA	NA	74 (4-year)	NA
JCOG9809	VCR, CPA, PSL, DOX	III	323[c]	NA	NA	74 (2-year)	12

CR, complete response; MST, median survival time; VCR, vincristine; CPA, cyclophosphamide; PSL, prednisone; DOX, doxorubicin; MTX, methotrexate; BLM, bleomycin; VDS, vindesine; ETP, etoposide; PCZ, procarbazine; NA, not applicable; R-II, randomized phase II study
[a]For high- and high-intermediate risk groups.
[b]For low- and low-intermediate risk groups.
[c]Number of enrolled patients until the early termination.

summarized. In addition, the results of new agent studies for lymphoid malignancies conducted in Japan are summarized, focusing on monoclonal antibody studies.

JCOG TRIALS FOR ADVANCED-STAGE AGGRESSIVE NHL

The results of consecutive JCOG trials for advanced aggressive NHL are summarized in Table 1. In 1981, LSG initiated the first randomized controlled study, JCOG8101, which compared VEPA [vincristine (VCR), cyclophosphamide (CPA, Endoxan™), prednisone (PSL) and doxorubicin (DOX)] and VEPA-M [VEPA plus methotrexate (MTX)] (2,3). One hundred and sixty-three untreated patients with advanced NHL, including 54 patients with ATL, were randomized. The complete response rate (%CR) and 4-year overall survival (OS) of 82 patients treated with VEPA-M were 62 and 37%, respectively, while for 81 patients treated with VEPA the rates were 52 and 27%, respectively. The difference between the two regimens was not significant; however, pretreatment variables predictive for efficacy were interesting. Three factors—leukemic change, poor performance status (PS) and T-cell phenotype—were negatively associated with both %CR and OS. In this study, the prognosis of patients with peripheral T-cell lymphoma (PTCL) other than ATL was comparable with that of B-NHL (2,3).

In 1987, against advanced aggressive NHL including ATL, JCOG-LSG initiated a phase II study (JCOG8701) of a non-cross resistant, alternating multi-agent chemotherapy of second generation, called LSG4, consisting of three regimens: (i) VEPA-B, i.e. VCR, CPA, PSL, DOX and bleomycin (BLM); (ii) M-FEPA, i.e. MTX, vindesine (VDS), CPA, PSL and DOX; (iii) VEPP-B, i.e. VCR, etoposide (ETP), procarbazine (PCZ), PSL and BLM (4). Between 1987 and 1991, 338 untreated patients were enrolled, and 267 (79%) of them were eligible. Central pathology review revealed 84 patients with T-NHL, including 42 with ATL, 151 with B-NHL and 33 with NHL of undetermined lineage (U-NHL). Overall, %CR was 72% (192/267): 81% (123/151) in B-NHL, 76% (25/33) in U-NHL, 66% (27/41) in PTCL other than ATL and 43% (18/42) in ATL. After the median follow-up of 56 months, estimated overall 5-year OS was 48%: 60% in B-NHL, 45% in U-NHL, 35% in PTCL and 12% in ATL. Unfavorable factors on OS that remained independently significant in Cox analyses were clinical diagnosis of ATL, total number of involved lesions ≥4, C-reactive protein (CRP)-positivity and Eastern Cooperative Oncology Group PS ≥ 2. JCOG8701 led to the following conclusions: (i) T-cell phenotype was an important pretreatment variable for aggressive NHL in Japan, (ii) LSG4 protocol was effective against B-NHL. Since the clinical diagnosis of ATL was an independent unfavorable factor, ATL patients were excluded from subsequent JCOG trials for aggressive NHL.

The aim of the subsequent JCOG9002 for aggressive NHL was to investigate survival benefit of dose-intensified multi-agent combination chemotherapy (5). Previously untreated patients with intermediate- or high-grade NHL according to the Working Formulation were eligible. Patients were randomly assigned to either dose-intensified multi-agent combination chemotherapy of the third generation, LSG9 (VEPA-B/FEPP-AB/M-FEPA every 10 weeks; three courses, 28 weeks in total) or the control arm combination chemotherapy of the second generation, modified LSG4 (mLSG4) (VEPA-B/FEPP-B/M-FEPA, every 14 weeks; four courses, 54 weeks in total). Planned dose intensity (DI)/week of DOX and CPA were 1.93- and 1.45-fold higher in LSG9 than in mLSG4, respectively.

Four hundred and forty-seven patients (230 in LSG9; 217 in mLSG4) were enrolled between 1991 and 1995. Pretreatment variables of the enrolled patients were well balanced between the two arms. Five-year OS was 57% for LSG9 and 55% for mLSG4 ($P = 0.42$). The %CR was 70% for LSG9 and 65% for mLSG4 ($P = 0.23$). Hematologic and non-hematologic toxicities of both regimens were equivalent and tolerable. Median

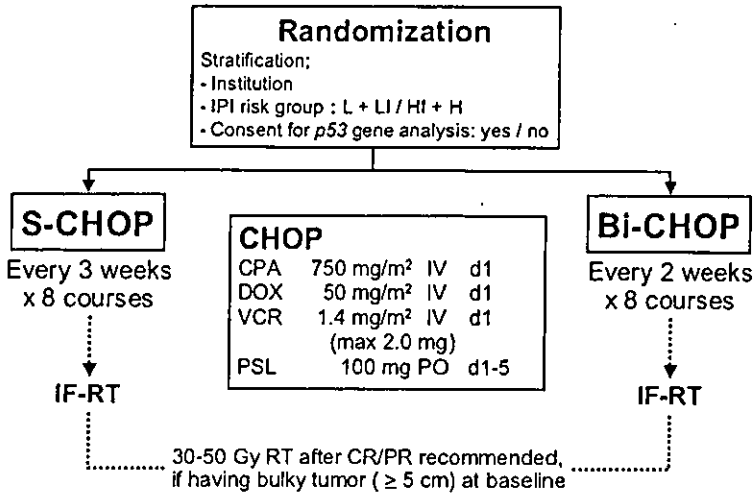

Figure 1. Study design of JCOG9809. Abbreviations: IPI, international prognostic index; L, low risk group; LI, low-intermediate risk group; HI, high-intermediate risk group; H, high risk group; S-CHOP, standard-dose CHOP therapy; Bi-CHOP, biweekly CHOP therapy; CPA, cyclophosphamide; DXR, doxorubicin; VCR, vincristine; PSL, prednisone; IV, intravenous administration; PO, per oral administration; d, day; IF-RT, involved-field radiotherapy; Gy, gray; RT, radiotherapy; CR, complete response; PR, partial response

actual DIs of DOX and CPA were 1.56- and 1.17-fold higher in LSG9 than in mLSG4, respectively. It was concluded that the increase in DI of DOX in multi-agent combination chemotherapy could not improve survival of aggressive NHL patients (5).

While conducting JCOG9002, the significant findings of an intergroup phase III study in the USA comparing CHOP (CPA, DOX, VCR, PSL) and three second- or third-generation regimens revealed that CHOP remains the best available treatment for first-line chemotherapy in advanced aggressive NHL (6). Other randomized controlled studies showed similar results. One potential explanation is that the addition of other myelosuppressive agents in second- or third-generation regimens results in a decrease in the DIs of the key agents for aggressive NHL such as DOX and CPA (7,8). Thus, JCOG-LSG changed the treatment strategy from the multi-agent chemotherapies to the dose-intensification of key agents.

There are two ways to increase the DI of CHOP, namely, dose-escalated and dose-dense strategies. The doses of DOX and CPA could be escalated with the prophylactic use of granulocyte colony-stimulating factor (G-CSF) (9). Another strategy is also possible with G-CSF, by shortening the treatment interval. In addition, the international prognostic index (IPI) was proposed as a predictive model for aggressive NHL, and the use of IPI was recommended for the design of future trials (10). Based on these findings, in 1995, JCOG-LSG initiated three kinds of phase II study according to IPI: JCOG9505 and JCOG9506 for high- and high-intermediate risk groups, and JCOG9508 for low- and low-intermediate risk groups. JCOG9506 is a phase II study of upfront, high-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (AHSCT), and JCOG9508 is a large-scale, phase II study of standard-dose CHOP therapy for lower risk patients.

Among them, the final results of JCOG9505 were published (11). The aim of the randomized phase II study, JCOG9505, was to explore a suitable dose-intensified regimen for the subsequent phase III study to compare with standard CHOP. Between 1995 and 1998, 70 patients with high-intermediate risk or high risk aggressive NHL according to IPI were enrolled and randomly assigned to receive either eight cycles of biweekly CHOP (CPA 750 mg/m^2, DOX 50 mg/m^2, VCR 1.4 mg/m^2 and PSL 100 mg for 5 days) every 2 weeks or six cycles of dose-escalated CHOP (CPA 1500 mg/m^2, DOX 70 mg/m^2, VCR 1.4 mg/m^2 and PSL 100 mg for 5 days) every 3 weeks. G-CSF was prophylactically administered. The primary endpoint was %CR.

The %CR was 60% [21/35; 95% confidence interval (CI), 42–76%] with biweekly CHOP and 51% (18/35; 95% CI, 34–69%) with dose-escalated CHOP. The major toxicity was grade 4 neutropenia and was more frequent in the dose-escalated CHOP (86%) than in the biweekly CHOP (50%). Grade 4 thrombocytopenia was also more frequent in the dose-escalated CHOP (20%) than the biweekly CHOP (3%). Non-hematologic toxicities were acceptable in both arms. One treatment-related death (due to cardiac arrhythmia) was observed in a dose-escalated CHOP patient. Progression-free survival (PFS) at 3 years was 43% (95% CI, 27–59%) in the biweekly CHOP arm and 31% (95% CI, 16–47%) in the dose-escalated CHOP arm. Similar %CR and PFS, but lower toxicity, suggested that biweekly CHOP is more promising for further investigations (11).

Based on the results of JCOG9505, in 1999 we initiated a phase III study, JCOG9809 (12). The study design of JCOG9809 is shown in Fig. 1. The primary purpose of JCOG9809 was to determine whether treatment results of aggressive NHL could be improved by shortening intervals of CHOP chemotherapy with the prophylactic use of G-CSF. The primary endpoint was PFS, and the planned accrual was 450. Until December 2002, 323 patients with advanced aggressive NHL were randomized to the standard CHOP arm (CHOP ×8,

Table 2. Results of JCOG trials for adult T-cell leukemia-lymphoma

Protocol/Regimen	Drugs	Phase	No. of patients	%CR (no.)	MST (months)	Survival (%)	Ref.
JCOG8101		III	54	28 (15/54)	7.5	8.3 (4-year)	2,3
LSG1-VEPA	VCR, CPA, PSL, DOX		24	17 (4/24)	NA	NA	
LSG2-VEPA-M	VCR, CPA, PSL, DOX, MTX		30	37 (11/30)	NA	NA	
JCOG8701	VCR, CPA, PSL, DOX, BLM, MTX, VDS, ETP, PCZ	II	42	43 (18/42)	8.0	12 (5-year)	4
JCOG9109	VCR, DOX, ETP, PSL, DCF	II	60	28 (17/60)	7.4	15.5 (2-year)	23
JCOG9303 (LSG15)	VCR, CPA, PSL, DOX, MCNU, VDS, ETP, CBDCA	II	93	35 (33/93)	13	31 (2-year)	24
JCOG9801		III	118	NA	NA	NA	NA
LSG15	VCR, CPA, PSL, DOX, MCNU, VDS, ETP, CBDCA, MTX, Ara-C						
LSG19	VCR, CPA, PSL, DOX, MTX, Ara-C						

%CR, complete response rate; MST, median survival time; NA, not applicable; DCF, 2'-deoxycoformycin; MCNU, ranimustine; CBDCA, carboplatin.

every 3 weeks) and biweekly CHOP arm (CHOP ×8, every 2 weeks). Major characteristics of 304 patients enrolled up to August 2002 were as follows: median age, 57 (range, 17–69); stage, 100 patients (33%) in II, 85 (28%) in III, 118 (39%) in IV (one ineligible for stage I); ECOG PS, 159 (52%) for 0, 120 (39%) for 1, 25 (8%) for 2; IPI, 128 (42%) for low risk group, 91 (30%) for the low-intermediate risk group, 62 (20%) for high-intermediate risk group, 23 (8%) for high risk group; histologic subtype according to the Working Formulation, 33 for D, 17 for E, 39 for F, 209 (69%) for G, 5 for H, 1 for J. Major prognostic factors, including the IPI risk group, were well balanced between the two arms.

The first planned interim analysis for 286 patients on December 18 2002 revealed that the PFS of the biweekly CHOP arm ($n = 143$) was slightly inferior to that of the standard CHOP arm ($n = 143$). The median PFS was 34 months in the standard CHOP arm and 24 months in the biweekly CHOP arm, and 2-year PFS was 54% in the standard CHOP arm and 51% in the biweekly CHOP arm. The hazard ratio of PFS between the arms was 1.10 (95% CI, 0.76–1.57). Two-year OS was 74% in the standard CHOP arm and 75% in the biweekly CHOP arm. Although there was one treatment-related death in the biweekly CHOP arm, toxicities of both regimens were equivalent and tolerable. According to the recommendations by the Data and Safety Monitoring Committee, JCOG9809 was terminated early, because it was deemed highly unlikely that the biweekly CHOP arm would be superior to the standard CHOP arm in PFS. It was concluded that a dose-dense strategy by interval shortening of CHOP chemotherapy was unable to prolong PFS in patients with aggressive NHL (12).

While we pursued the dose-intensified CHOP strategies, a chimeric anti-CD20 monoclonal antibody, rituximab, was clinically developed for the treatment of B-NHL (13–16). Rituximab as a single agent was found to be effective not only for indolent B-NHL but also for aggressive B-NHL (17,18). More importantly, a phase III study comparing rituximab plus CHOP (R-CHOP) and CHOP for untreated elderly patients with diffuse large B-cell lymphoma (DCBCL) revealed that the efficacy of R-CHOP is superior to CHOP (19). Based on these findings, JCOG-LSG is currently planning future trials of rituximab-containing combination chemotherapy with the aim of improving the efficacy of R-CHOP further against aggressive B-NHL.

JCOG TRIALS AGAINST ADULT T-CELL LEUKEMIA-LYMPHOMA (ATL)

ATL is defined as a peripheral T-cell malignancy caused by an RNA retrovirus, human T-cell leukemia virus type I. Acute-type ATL has characteristic clinical and laboratory findings, including flower cells in peripheral blood, hypercalcemia and frequent organ involvement such as the skin, gastro-intestinal tract, lung and central nervous system. Four clinical subtypes such as acute-, lymphoma-, chronic- and smoldering-type have been recognized (20).

The main results of the JCOG trials for ATL are summarized in Table 2. In the phase III trial, JCOG8101, which compared VEPA versus VEPA-M against advanced NHL including ATL between 1981 and 1983, the %CR of VEPA-M for ATL (37%) was higher than that of VEPA (17%) ($P = 0.09$) (2,3). However, the %CR was significantly lower for ATL than for B-NHL and PTCL other than ATL ($P < 0.001$). The median survival time (MST) of 54 patients with ATL treated with VEPA or VEPA-M was only 7.5 months, and the estimated 4-year OS was only 8%.

In the subsequent phase II study (JCOG8701) of a multi-agent combination chemotherapy, the %CR for ATL patients (43%, 18/42) was improved from 28% (15/54) in JCOG8101; however, the %CR was significantly lower in ATL than in B-NHL and PTCL ($P < 0.01$) (4). Patients with ATL showed the most unfavorable prognosis with an MST of 8 months and a 5-year OS of 12%. A multivariate analysis demonstrated that the clinical diagnosis of ATL was the most significant unfavorable prognostic factor (4).

The disappointing results against ATL with conventional chemotherapies have led to the search for new active agents. Deoxycoformycin (DCF), an inhibitor of adenosine deami-

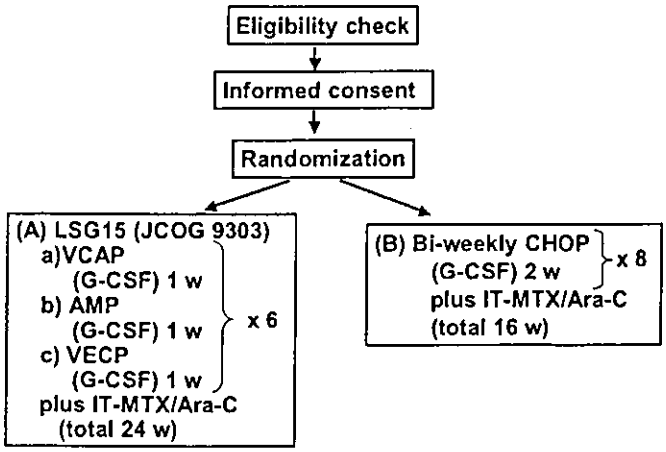

Figure 2. Study design of JCOG9801. Abbreviations: VCAP, vincristine + cyclophosphamide + doxorubicin + prednisolone; AMP, doxorubicin + ranimustine + prednisone; VECP, vindesine + etoposide + carboplatin + prednisolone; IT, intrathecal administration; MTX, methotrexate; Ara-C, cytosine arabinoside; G-CSF, granulocyte colony-stimulating factor; w, week

nase, was reported to be effective in a number of lymphoid malignancies. Based on the promising results of some single-institute studies, multicenter phase I and II studies of DCF were conducted against ATL in Japan (21,22). The phase II study revealed a response rate of 32% (10/31) in relapsed or refractory ATL, using the weekly intravenous administration of 5 mg/m^2. These encouraging results prompted us to conduct a DCF-containing combination phase II trial (JCOG9109) as an initial chemotherapy for ATL (23). Between 1991 and 1993, 62 untreated patients with ATL (34 acute, 21 lymphoma and seven chronic types) were enrolled. VCR 1 mg/m^2 intravenously (IV) on days 1 and 8, DOX 40 mg/m^2 IV on day 1, ETP 100 mg/m^2 IV on days 1–3, PSL 40 mg/m^2 per os on days 1 and 2 and DCF 5 mg/m^2 IV on days 8, 15 and 22 were administered every 28 days for 10 cycles unless disease progression occurred. Among the 61 patients evaluable for toxicity, four patients (7%) died of fatal infections such as sepsis and cytomegalovirus pneumonia. In the 60 eligible patients, there were 17 CRs (28%) and 14 PRs [overall response rate (ORR) 52%]. The MST was 7.4 months, and the estimated 2-year OS was 17%, findings that were identical to those of the 42 patients with ATL who were treated in JCOG8701. It was concluded that the prognosis of patients with ATL remained poor even when treated with a DCF-containing combination chemotherapy (23).

In 1994, JCOG-LSG initiated a new multi-agent combination phase II trial (JCOG9303; LSG15): an eight-drug regimen consisting of VCR, CPA, DOX, PSL, ranimustine (MCNU), VDS, ETP and carboplatin (CBDCA), for untreated ATL (24). The elevation of relative DI was attempted with the prophylactic use of G-CSF. In addition, non-cross-resistant agents such as MCNU and CBDCA were incorporated to overcome the multidrug resistance of ATL cells. Ninety-six untreated patients with aggressive ATL were enrolled: 58 patients with acute type, 28 with lymphoma type and 10 with unfavorable chronic type. Eighty-one percent of the 93 eligible patients responded (75/93), with 33 patients obtaining CR (35%) and 42 PR (45%). The OS of 93 eligible patients at 2 years was 31%. The MST was 13 months and the median follow-up duration of the 20 surviving patients was 4.2 years. A trend towards better OS for lymphoma-type patients (MST, 20 months) compared with acute-type patients (MST, 11 months) was recognized (hazard ratio, 1.65). Grade 4 hematologic toxicities of neutropenia and thrombocytopenia were observed in 65% and 53% of the patients, respectively, but grade 4 non-hematologic toxicity was observed in only one patient. It was concluded that the LSG15 is feasible and improved the clinical outcome of patients with ATL (24). To confirm whether the LSG15 is a new standard for the treatment of aggressive ATL, JCOG-LSG has conducted a phase III study, JCOG9801, comparing the LSG15 with biweekly CHOP (Fig. 2). Patient enrollment into this phase III study was completed in October 2003.

JCOG TRIALS AGAINST HODGKIN'S LYMPHOMA

Since Hodgkin's lymphoma is not common in Japan, JCOG-LSG has conducted consecutive phase II studies to confirm the applicability of the commonly used or standard combination chemotherapy regimens, which were established in Western countries, to Japanese patients with Hodgkin's lymphoma. The main results of JCOG trials for Hodgkin's lymphoma are summarized in Table 3.

Between 1989 and 1993, JCOG-LSG conducted a phase II study (JCOG8905) of alternating combination chemotherapy C-MOPP (CPA, VCR, PCZ, PSL) and ABVd [DOX, BLM, vinblastine (VLB), dacarbazine (DTIC)] for clinical stages II–IV Hodgkin's lymphoma (25). [Note that CPA was substituted for mechlorethamine (in MOPP), since the latter was not commercially available in Japan.] A two-thirds dose (250 mg/m^2) of DTIC was used, because a full dose (375 mg/m^2) of DTIC

Table 3. Results of JCOG trials for advanced Hodgkin's lymphoma

Protocol/Regimen	Drugs	Phase	No. of patients	%CR (no)	PFS (%)	Survival (%)	Ref.
JCOG8905 (C-MOPP/ABVd)	CPA, VCR, PCZ, PSL, DOX, BLM, VLB, DTIC	II	79	84 (56/67)	73 (4-year)	85 (5-year)	25
JCOG9305 (ABVd)	DOX, BLM, VLB, DTIC	II	128	78 (100/128)	75 (5-year)	89 (5-year)	27
JCOG9705 (ABV)	DOX, BLM, VLB	II	72[a]	72 (33/46)	51 (2-year)	92 (2-year)	28

PFS, progression-free survival; VLB, vinblastine; DTIC, dacarbazine.
[a]No. of enrolled patients until the early termination.

was intolerable owing to severe emesis at that time. The full chemotherapy schedule for both regimens was five courses each. Patients with bulky disease were given involved-field radiotherapy (30 Gy) after completion of chemotherapy. Seventy-nine untreated patients were enrolled. For 67 eligible patients, the ORR was 93% with 84% CR. Five-year OS was 85%, and 4-year PFS was 73%. Grade 4 toxicity consisted of leukopenia in 28% of patients, but there were no treatment-related death. It was concluded that the C-MOPP/ABVd regimen is one of the effective regimens for Japanese patients with advanced Hodgkin's lymphoma (25).

In 1992, Canellos et al. reported the significant results of a phase III study conducted by Cancer and Leukemia Group B (CALGB) which compared MOPP (mechlorethamine, VCR, PCZ, PSL), ABVD or MOPP alternating with ABVD (26). Thereafter, ABVD was regarded as a standard therapy for advanced Hodgkin's lymphoma because of high efficacy and low short-term and long-term toxicities. Based on the results of the CALGB study (26) and our own preceding JCOG8905 (25), JCOG-LSG conducted a phase II study (JCOG9305) to investigate the efficacy and toxicity of ABVd therapy in Japanese patients with advanced Hodgkin's lymphoma (27). Between 1993 and 1997, a total of 128 patients with advanced-stage Hodgkin's lymphoma were enrolled and received ABVd with six or eight courses. Bulky tumors were irradiated after chemotherapy at 30–40 Gy. The CR was 78% (100/128; 95% CI, 70–85%). Major toxicity was grade 4 neutropenia (45%). Non-hematologic toxicities were acceptable; the most frequent toxicity of grade ≥3 was nausea/vomiting (11%), and grade 4 toxicity was observed in only one patient who developed ileus. OS and PFS at 5 years were 89% (95% CI, 83–95%) and 75% (95% CI, 67–83%), respectively. It was concluded that ABVd therapy is effective in Japanese patients with advanced-stage Hodgkin's lymphoma (27).

In ABVD or ABVd therapy, gastrointestinal toxicity and phlebitis are frequent adverse events associated with DTIC; however, the evidence of efficacy of DTIC for Hodgkin's lymphoma is insufficient compared with the three other agents. To explore a less toxic and equally effective regimen, JCOG-LSG conducted a multicenter phase II study (JCOG9705) of 'ABV' deleting DTIC followed by involved-field radiotherapy (28). The primary endpoint was %CR. Between 1998 and 2000, 72 patients were enrolled and received six or eight courses of 'ABV' with increased dose of DOX (DOX 30 mg/m^2, days 1 and 15; BLM 9 mg/m^2, day 1 and 15; VLB 6 mg/m^2, day 1 and 15). Residual tumors of PR cases and bulky tumors were irradiated after chemotherapy. The first planned interim analysis revealed that 2-year PFS (51%; 95% CI, 39–63%) was significantly inferior to the 80% of our historical control, JCOG9305 (ABVd), although %CR (71%; 95% CI, 58–82%) was equal. According to the recommendations by the Data and Safety Monitoring Committee, patient enrollment was interrupted. In conclusion, the early results of JCOG9705 suggested that the efficacy of ABV with increased dose of DOX and deleted DTIC was inferior to ABVd. It is also suggested that DTIC is a key agent in ABVD therapy (28).

DEVELOPMENT OF NEW ANTICANCER AGENTS FOR NHL AND ATL

IRINOTECAN HYDROCHLORIDE (CPT-11)

CPT-11 is a semisynthetic analog of camptothecin with inhibitory activity against topoisomerase I. CPT-11 has definitive activity against various kinds of solid tumors. Multicenter phase II studies of CPT-11 were conducted against relapsed or refractory NHL in Japan (29–31). The pivotal study revealed nine CRs and 17 PRs (ORR 38%, 26/69), using a weekly intravenous administration of 40 mg/m^2/day for 3 consecutive days (30). In that study, five (38%) of 13 patients with ATL showed a response to CPT-11 (one CR and four PRs) (31).

To develop a new effective chemotherapy regimen against NHL and ATL, we conducted two kinds of phase I/II study of CPT-11 in combination with CBDCA or ETP for relapsed or refractory NHL (32,33). However, in both studies, dose-escalation was halted because of hematologic toxicity in combination with CBDCA and hepatotoxicity in combination with ETP.

Daiichi Pharmaceutical Co. Ltd, Tokyo, Japan, supported the trials of CPT-11.

INTERFERON-α

Based on the preliminary documentation of the efficacy of interferon-α against ATL, two kinds of phase I/II trial of high-dose interferon-α (intravenous and subcutaneous administrations) were conducted in Japan; however, the results were not impressive (unpublished data). In 1995, Gill et al. in the USA reported that 11 of 19 patients with acute- or lymphoma-type ATL achieved major responses (five CRs and six PRs) by the combination therapy of interferon-α and zidovudine (34). The efficacy of this combination was also observed in a French study; the major objective responses were obtained in all five ATL patients (35). Although the results of this combination were encouraging, the OS of previously untreated ATL patients was relatively short (4.8 months) (4,36) compared with those in the chemotherapy trials by the JCOG-LSG (7–13 months) (2–4,23,24). Furthermore, the %CR associated with the use of interferon-α and zidovudine in previously untreated patients (25%, 3/12) was not superior to the %CR in those treated with the JCOG-LSG chemotherapy protocols (28–42%). In 2001, White et al. reported the results of this combination in 18 patients with ATL mostly pretreated with radioimmunotherapy and only three of them (17%) showed objective responses (37).

The clinical trials of interferon-α in Japan were supported by Sumitomo Pharmaceuticals, Osaka, Japan.

CLADRIBINE (2-CHLORODEOXYADENOSINE, 2-CdA)

Cladribine is a chlorinated purine analog resistant to adenosine deaminase. Cladribine was found to be effective against hairy cell leukemia (HCL), B-chronic lymphocytic leukemia, indolent B-NHL and cutaneous T-cell lymphoma. In a Japanese phase I study of cladribine, one relapsed patient with ATL achieved PR (38). A multicenter phase II study of cladribine

against relapsed or refractory ATL was conducted in Japan (39). Cladribine was administered as 0.09 mg/kg/day by 7-day continuous intravenous infusion every 28 days up to three courses. However, since the interim analysis revealed that only one of the 15 eligible patients showed PR (ORR 7%; 90%, CI 0–28%), the phase II study for ATL was terminated.

Cladribine was also evaluated for relapsed or refractory indolent NHL in Japan (40). Between 1996 and 1999, 45 previously treated patients with indolent NHL were enrolled, of which 43 were eligible. The median number of prior chemotherapy regimens was 2 (range, 1–14). Central pathology review revealed that 34 patients had follicular, three mantle cell lymphoma (MCL), three marginal zone B-cell lymphoma, two mycosis fungoides and one macroglobulinemia. The median number of administered cycles of cladribine was 3 (range, 1–6). The ORR was 58% (25/43; 95% CI, 45–71%) with 14% CR (6/43; 95% CI, 6–26%). The median time to progression (TTP) in 25 responders was 9 months (range, 1–31+). Neutropenia and thrombocytopenia of grade ≥3 were observed in 53% (24/45) and 38% (17/45), respectively. Prolonged (≥180 days) neutropenia and/or thrombocytopenia of grade ≥3 were observed in 27% (12/45), and they persisted up to 419+ days. Five patients (11%) developed infections of ≥ grade 3, including two treatment-related deaths (systemic herpes simplex virus infection and pulmonary aspergillosis). Other non-hematologic toxicities were acceptable. Four patients developed myelodysplastic syndrome after the completion of cladribine treatments. It was concluded that cladribine is an active agent in the treatment of refractory or relapsed indolent NHL with durable major responses. Toxicity was acceptable, but prolonged myelosuppression and myelodysplastic syndrome should be carefully monitored (40). In the phase II study for HCL, we obtained a high response rate (70%, 7/10). In 2002, cladribine was approved for HCL and indolent B-NHL in Japan.

Janssen Pharma Co. Ltd, Tokyo, Japan, supported the clinical trials of cladribine.

Fludarabine Phosphate

Fludarabine, another purine analog, is presently being evaluated for indolent B-NHL in Japan. Intravenous (IV) fludarabine demonstrated marked efficacy for indolent B-NHL; however, 5-day IV administration is inconvenient in an outpatient setting. The primary objective of a Japanese phase I study of oral fludarabine was to investigate its tolerability, efficacy and pharmacokinetic profile in relapsed or refractory patients with indolent B-NHL (41). Twelve relapsed patients, including 10 with follicular lymphoma and two with MCL, were enrolled. Their median age was 57, and the median number of prior regimens was two. They received 30, 40 or 50 mg/m^2/day for 5 consecutive days every 4 weeks, for a total of one to three cycles (three patients for 30 mg/m^2/day; six patients for 40 mg/m^2/day; three patients for 50 mg/m^2/day). One of the six patients treated at 40 mg/m^2/day developed grade 4 hyperuricemia, and one of the three patients treated at 50 mg/m^2/day developed grade 4 febrile neutropenia. Another patient treated at 50 mg/m^2/day required G-CSF due to grade 4 neutropenia. In total, grade ≥3 toxicities were leukopenia (50%), neutropenia (50%), lymphopenia (83%) and hyperuricemia (8%). All the encountered toxicities were reversible. According to the international workshop criteria, the ORR was 67% (8/12) (1/3 for 30 mg/m^2/day; 4/6 for 40 mg/m^2/day; 3/3 for 50 mg/m^2/day). Based on area under the curve (AUC) values of the fifth day, the mean systemic bioavailability of 63% (78% for 30 mg/m^2/day; 58% for 40 mg/m^2/day; 56% for 50 mg/m^2/day) obtained in Japanese patients was similar to that in Caucasians. It was concluded that oral fludarabine is safe and effective for relapsed patients with indolent B-NHL. To assess the efficacy and toxicity of oral fludarabine in relapsed indolent B-NHL further, we are currently conducting a pivotal phase II study using the dose of 40 mg/m^2/day.

Nihon Schering K.K., Osaka, Japan, supported the clinical trials of fludarabine phosphate.

DEVELOPMENT OF MONOCLONAL ANTIBODY THERAPIES FOR B-NHL1

Rituximab

Rituximab is a chimeric monoclonal antibody, with mouse variable and human constant regions, that recognizes the CD20 antigen (42).

Feasibility and Pharmacokinetic Study of Rituximab

The feasibility of rituximab administration in Japanese patients with relapsed B-NHL was evaluated at 250 mg/m^2 and 375 mg/m^2 per infusion under the administration schedule of four consecutive weekly infusions (14). Four patients received the rituximab 250 mg/m^2 infusion and eight the 375 mg/m^2 infusion. The majority of patients (8/11) had lymphoma with follicular histology. All encountered non-hematologic toxicities were of grade 2 or less. The commonly observed toxicities of rituximab were fever (6/11), chills/rigor (4/11), rash/urticaria (3/11), pruritus (3/11) and perspiration (3/11). Of 11 eligible patients, seven developed hematologic toxicities, but none was grade 4. Peripheral blood B cells decreased to 0–2% of the total lymphocyte counts within 48 h after the first infusion. There were no significant changes in T-cell counts, or in serum immunoglobulin and complement C3 levels. Human anti-murine antibody (HAMA) and human anti-chimeric antibody (HACA) were not detected.

Of the three patients who received rituximab 250 mg/m^2, two achieved objective responses (one CR and one PR). In the eight patients who received rituximab 375 mg/m^2, five achieved objective responses (one CR and four PRs).

The mean values [± standard deviation] of the trapezoidal AUC and maximum concentration (C_{max}) in the 375 mg/m^2 dose group were 118 237 ± 53 412 μg/ml h and 92.1 ± 34.3 μg/ml, respectively, which were higher than those in the 250 mg/m^2 dose group (91 343 ± 70 267 μg/ml h and 64.3 ± 21.4 μg/ml). The serum elimination half-life ($T_{1/2}$) was 445.4 ±

361.4 h (18.6 ± 15.8 days). The mean peak and trough levels of rituximab at each infusion increased in parallel with the course of infusion. The serum levels of rituximab were detectable at 3 months after the final infusion in most patients. It was concluded that the dose of four, once weekly 375 mg/m^2 IV infusions of rituximab was safe and effective in Japanese patients with relapsed or refractory B-NHL (14).

Single-agent Phase II Study in Relapsed Indolent B-NHL and MCL

Ninety patients with indolent B-NHL or MCL who had relapsed or were resistant to prior conventional chemotherapy were enrolled and divided into two groups: group I comprised patients with indolent B-NHL and group II patients with MCL (16). A central pathology review was performed for biopsy specimens from 86 (96%) of the 90 patients enrolled in the study, according to the Revised European–American Lymphoma (REAL) Classification. Immunohistochemical analyses were conducted using anti-CD20, anti-CD3, anti-bcl-2 and anti-cyclin-D1 antibodies. Follicular lymphoma accounted for 83% in group I-enrolled patients.

The most commonly observed non-hematologic toxicities were infusion-related symptoms such as fever, chills/rigor, nausea/vomiting, rash, pruritus, perspiration, asthenia, headache, pain and urticaria, which mainly did not exceed grade 2. These symptoms generally occurred during the first infusion and decreased with subsequent infusions. All non-hematologic toxicities were reversible. Grade 3 or 4 hematologic toxicities were observed in 23 patients (26%). Five patients (6%) developed grade 4 neutropenia, two (2%) developed grade 3 thrombocytopenia and one (1%) grade 4 thrombocytopenia. Seven episodes of infection were noted within 6 months after rituximab administration, of which five were grade 1. All patients except two exhibited a marked decrease in peripheral blood CD19+ and CD20+ cells after the first rituximab infusion. The decrease in B cells continued for at least 3 months, but showed a gradual recovery up to 6 months or thereafter. Of the 90 patients who received rituximab infusion, four developed HACA. In three patients, the HACA levels were below the quantifiable limit (3.9 ng/ml) by the enzyme-linked immunosorbent assay (ELISA), while in one patient the HACA levels were 398 ± 53 ng/ml.

The ORR in 61 eligible patients in group I (indolent B-NHL) was 61% (95% CI, 47–73%), including 14 patients (23%) who achieved CR and 23 patients (38%) who achieved PR. The ORR in the 13 eligible patients in group II (MCL) was 46% (95% CI, 19–75%), and all six responders achieved PR. The median PFS interval in groups I and II was 245 and 111 days, respectively.

Pretreatment factors affecting ORR and PFS were analyzed in 77 patients whose histopathology was centrally confirmed as indolent B-NHL or MCL. The ORR was significantly affected by the number of prior chemotherapy regimens (P = 0.02). Multivariate analysis demonstrated that MCL, extranodal disease, and number of prior chemotherapy regimens were unfavorable factors affecting PFS (all $P < 0.05$). The PFS intervals of patients with higher serum rituximab levels (≥70 μg/ml) immediately before the third infusion were longer than other patients ($P < 0.05$).

In summary, rituximab is a highly effective agent in relapsed indolent B-NHL and MCL with acceptable toxicities. Rituximab is more effective in the treatment of relapsed indolent B-NHL than of MCL, and in patients without extranodal disease or with a history of having received only one prior chemotherapy regimen. Several prognostic factors and serum rituximab levels are useful in predicting the efficacy of rituximab monotherapy (16).

Subsequent Clinical Trials of Rituximab in Japan

In 1999, two multicenter phase II studies were initiated in Japan: a single-agent phase II study in recurrent aggressive B-NHL (18), and a randomized phase II study of rituximab in combination with CHOP, comparing concurrent and sequential administration in previously untreated advanced-stage indolent B-NHL (43).

In the single-agent phase II study of rituximab for recurrent aggressive B-NHL, a total of 68 patients with REAL types II-3, 9, 10 and 11 were enrolled and treated with rituximab 375 mg/m^2, weekly for 8 consecutive weeks (18). A central pathology review disclosed that 57 patients (84%) were eligible. The Independent Computed Tomography Review Committee confirmed that ORR was 35% (24/68) in enrolled patients and 37% (21/57) in eligible patients. The median PFS of the 53 evaluable patients was 52 days, whereas the time to progression of the 21 eligible responders was 245 days. The encountered toxicities of rituximab were transient and most were of grade 1 or 2. Serum samples were collected for pharmacokinetic analysis in 12 patients. There was a steady increase in the peak and trough rituximab levels at all time points during the eight consecutive weekly treatments. It was concluded that rituximab monotherapy with eight consecutive weekly infusions showed significant anti-lymphoma activity in aggressive B-NHL with acceptable toxicities (18).

After the approval of rituximab in Japan in 2001, three kinds of new trials incorporating rituximab were initiated or are currently in preparation. One is a phase II/III study of rituximab in combination with CHOP and biweekly CHOP for untreated advanced-stage, indolent B-NHL (JCOG0203). In the biweekly CHOP arm, an augmenting effect of antibody-dependent cell-mediated cytotoxicity (ADCC) of rituximab is expected. Another study in preparation is a phase II study of HDC with AHSCT for untreated MCL, which expects to show an *in vivo* purging effect of rituximab. The third study in preparation is a phase II/III study of rituximab in combination with CHOP for untreated diffuse large B-cell lymphoma, comparing weekly and tri-weekly administrations of rituximab. A schematic representation of the clinical trials of rituximab in Japan is shown in Fig. 3.

Zenyaku Kogyo Co., Ltd, Tokyo, Japan, supported the clinical trials of rituximab.

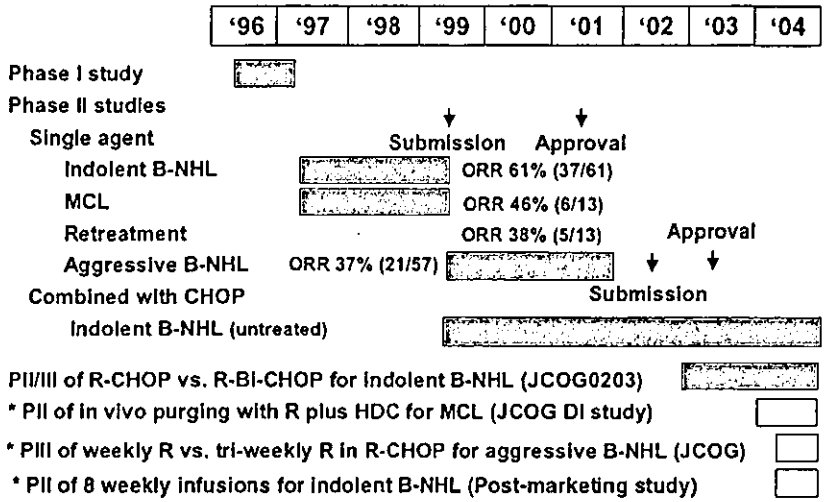

Figure 3. Schematic representation of the clinical trials of rituximab in Japan. *Study in which patient enrollment has not yet been initiated. Abbreviations: ORR, overall response rate; B-NHL, B-cell non-Hodgkin's lymphoma; MCL, mantle cell lymphoma; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; PII, phase II study; PIII, phase III study; PII/III, phase II/III study; R, rituximab; HDC, high-dose chemotherapy; Submission, submission of the data of licensing study to the Ministry of Health, Labor and Welfare; Approval, approval for the use under the National Health Insurance in Japan; DI study, data center-independent study.

IBRITUMOMAB TIUXETAN (ZEVALIN™)

Ibritumomab is a murine anti-CD20 monoclonal antibody that was engineered to form rituximab. Tiuxetan is a MX-DTPA linker chelator that is attached to ibritumomab to form ibritumomab tiuxetan (Zevalin™). The ibritumomab tiuxetan is radiolabeled with either ^{111}In (^{111}In-Zevalin) for dosimetry studies or with ^{90}Y (^{90}Y-Zevalin) for therapy of B-NHL (44). In 2002, a feasibility study of ibritumomab tiuxetan was initiated in Japan, and patient enrollment was completed in August 2003. We are planning a subsequent pivotal phase II study.

Nihon Schering K.K., Osaka, Japan, supported the clinical trials of fludarabine phosphate.

CONCLUSIONS

The present status of the JCOG-LSG trials and industry-supported new agent studies for malignant lymphoma mainly conducted by the members of the JCOG-LSG are summarized. JCOG-LSG has conducted 21 multicenter trials, focusing on aggressive NHL and ATL. In the treatment of advanced aggressive NHL, we investigated the efficacy of G-CSF-supported dose-intensified strategies. Based on the results of a randomized phase II study (JCOG9505), we conducted a phase III study, JCOG9809, comparing CHOP and biweekly CHOP. However, JCOG9809 was terminated early based on the results of a planned interim analysis, because it was deemed highly unlikely that biweekly CHOP would be superior to standard CHOP. For aggressive ATL, a dose-intensified, multi-agent regimen (JCOG9303; LSG15) showed superior efficacy to our historical controls. To establish a new standard for ATL, we have conducted a phase III study, JCOG9801, comparing the LSG15 and biweekly CHOP. New agent development for malignant lymphoma in Japan has been focused on irinotecan, DCF, cladribine, oral fludarabine and rituximab, and encouraging results have been obtained. The multicenter trials by the JCOG-LSG and industry-supported new agent studies will contribute to the further improvement in the treatment of malignant lymphoma.

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