録し、プロトコールに従って治療を施行した。適格例に対しては、引き続き積極的に説明と同意を進め症例登録に努力している。

D．考察

本研究の対象疾患である進行期低悪性度B細胞リンパ腫に対して、現在まで、他の治療法に比し生存期間を有意に延長する初期治療のevidenceが存在しないことから、至適治療をめぐってこれまで議論が多かった。

今回我々は本疾患患者を対象に、数年先に標準治療となる確率の高いリツキシマブとCHOP 療法との併用療法 (R-CHOP)を対照治療群とし、化学療法の用量強度増強とG-CSF併用によるリツキシマブの効果増強が期待されるbiweekly CHOP療法をリツキシマブに併用する併用療法 (R･Bi-CHOP)を試験治療群として採択する形のランダム化比較試験を計画した。

高齢者びまん性大細胞型Bリンパ腫に対するR-CHOPとR･Bi-CHOPの比較試験で後者が優れていることが2005年の第47回American Society of Hematologyにおいてドイツから報告された。一方、進行期低悪性度B細胞リンパ腫に対するR･Bi-CHOPの成績はこれまで報告されていない。

本臨床研究は登録が開始されてから約3年半が経過したが、登録ペースは予定を上回っている。

E．結論

本臨床試験は開始されてから約3年が経過したが、症例の登録ペースは予定を上回っている。本研究によって、進行期低悪性度B細胞リンパ腫に対する、新たな標準治療確立と当該疾患患者の予後改善が期待される。

F．健康危険情報

なし。

G. 研究発表

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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 17 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

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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

（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（JCOG0203-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 6 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し、さらにホジキン病におけるＣＣＲ４陽性細胞の意義を検討する。

B. 研究方法：ケモカイン受容体である CCR4 の発現を KM2160 抗体を用いて免疫染色で検討した。ＣＴＣＬに対して抗ＣＣＲ４抗体による細胞増殖抑制効果を、in vitro で評価した。また、ホジキン病細胞のＣＣＲ４のリガンドの産生量を定量化し、CCR4 陽性 Treg 細胞の誘導能を調べた。

C. 研究結果：低フコース型キメラ型抗 CCR4 抗体が成人 T 細胞性白血病・リンパ腫

(ATLL) に対し、強い抗腫瘍効果を示すことを報告してきた。免疫染色の結果、CCR4 が cutaneous T cell lymphoma (CTCL)の約半数に発現し、抗 CCR4 抗体は患者末梢血単核球存在下で CTCL 細胞に強い ADCC を誘導した。以上より抗 CCR4 抗体が CTCL に対する有望な新規抗体療法になり得る事を示した。また、ホジキンリンパ腫細胞は TARC/CCL17、MDC/CCL22 を産生することで腫瘍周囲に CCR4 陽性 Treg 細胞を能動的に集束させ、生体内で宿主の免疫監視機構から逃れていることを証明し、抗 CCR4 抗体が CD4+CD25+CCR4+陽性 Treg 細胞を depletion させ免疫監視機構回避を不可能にすることでホジキンリンパ腫に対する有望な新規抗体療法になり得る事を示した。

D. 考察： ATLL のみならず CCR4 陽性ＣＴＣＬ、あるいはホジキン病にも抗 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ＣＴＣＬ、ホジキン病に対しても抗ＣＣＲ４抗体療法の応用が期待されさらに開発を進める努力が必要である。

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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。

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１７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

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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 2 症例を登録し、合計 12 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 3 1 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 2 症例を登録し（合計 12 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。

本年度は 2 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 12 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。現時点で少数例を外来治療室にて

施行しているが、G-CSF の投与に関しては、かかりつけ医と協力して遂行できる体制が望まれる。

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 陽性患者様ならびに HBcAb 高値の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。このことは、全国がん協議会の主催によるテレビ討論会にて発表した。

（参考）多地点合同メディカル・カンファレンス［2005-第 34 回］

日　時：2005 年 11 月 17 日(木) 16：30～18：00

テーマ：化学療法／造血幹細胞移植に伴う

B 型肝炎ウイルスの再活性化について

（新潟県立がんセンター新潟病院主管）

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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2）鈴木孝世：　What's going on (GELA Study). Mebio Oncology 2:112-115, 2005.

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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ORIGINAL REPORT

Phase II Study of Oral Fludarabine Phosphate in Relapsed Indolent B-Cell Non-Hodgkin's Lymphoma

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

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ABSTRACT

Purpose
Although intravenous (IV) fludarabine phosphate is effective against indolent B-cell non-Hodgkin's lymphoma (B-NHL), IV administration for 3 to 5 consecutive days is inconvenient in an outpatient setting. To assess the efficacy and toxicity of oral fludarabine phosphate in patients with indolent B-NHL, we conducted a multicenter phase II study.

Patients and Methods
Patients with relapsed indolent B-NHL received fludarabine phosphate tablets orally once daily on days 1 through 5 every 28 days for three to six cycles. The efficacy was separately analyzed in a mantle-cell lymphoma (MCL) cohort and indolent B-NHL except for MCL (IL) cohort. The primary end point was the overall response rate (ORR).

Results
Fifty-two patients, including 46 in the IL cohort (41 with follicular lymphoma) and six in the MCL cohort, were registered, and all patients were eligible. Forty-one patients (79%) had received rituximab as prior therapy. In the IL cohort, the ORR and complete response rate were 65% (30 of 46 patients; 95% CI, 50% to 79%) and 30% (14 of 46 patients; 95% CI, 18% to 46%), respectively. One of six patients with MCL achieved a partial response. The median times to treatment failure for the 46 patients in the IL cohort and for the six patients in the MCL cohort were 8.6 and 6.1 months, respectively. Hematologic toxicities, including grade 4 neutropenia (37%), were the most frequent toxicities, and nonhematologic toxicities were mild.

Conclusion
Oral fludarabine phosphate is highly effective in patients with relapsed indolent B-NHL who have mostly been pretreated with rituximab and is more convenient than the IV formulation.

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INTRODUCTION

The majority of patients with indolent B-cell non-Hodgkin's lymphoma (B-NHL), mainly consisting of follicular lymphoma, are incurable by current treatments. Most patients initially respond to chemotherapy, but the clinical course follows a pattern of repeated relapse. The disease has a relatively long natural history, with a median survival time of 7 to 10 years.[1] Thus, effective treatment that maintains a good quality of life is warranted.

The use of alkylating agents as monotherapy or in combination has been one of the most frequently applied treatments for patients with indolent B-NHL. Cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy did not show therapeutic superiority to treatment without doxorubicin.[2] Recent improvements have included rituximab, a chimeric anti-CD20 monoclonal antibody, which has activity as a single agent[3,4] and in combination.[5,6] Except for chlorambucil and oral cyclophosphamide, these treatments are administered by intravenous (IV) infusion, and frequent visits to the outpatient clinic are required. For this indolent disease, effective oral therapy is preferable.

Fludarabine phosphate is a purine analog that has a high efficacy for B-cell chronic lymphocytic leukemia as an IV formulation.[7] In addition, using the dose and schedule of 18 to 30 mg/m^2/d daily for 5 days, every 3 to 5 weeks, IV fludarabine has shown overall response rates (ORRs) ranging from 27% to 65%, with response durations of 10 to 12 months, as a monotherapy for selected patients with relapsed indolent NHL[8-11] and exhibited a better progression-free survival than cyclophosphamide, vincristine, and prednisone.[12] The oral form

of fludarabine phosphate has a bioavailability of 55%,[13] and in a phase II study for B-cell chronic lymphocytic leukemia, using fludarabine 10-mg tablets at a dose of 40 mg/m^2/d for 5 days, repeated every 4 weeks, the ORR (51%, 40 of 78 patients) was similar to the ORR of IV fludarabine.[14] Therefore, it is expected that oral fludarabine is effective for indolent B-NHL.

In Japan, a phase I study of oral fludarabine was conducted on 12 patients with relapsed indolent B-NHL.[15] The mean bioavailability of 63% obtained in Japanese patients was similar to the 55% bioavailability obtained in whites.[13] Objective responses were observed in eight of the 12 patients. Given the toxicity profiles, the recommended dose for the subsequent phase II study was set at 40 mg/m^2/d daily for 5 days every 4 weeks.[15] To further assess the efficacy and toxicity of oral fludarabine phosphate in patients with relapsed indolent B-NHL, we conducted a multicenter phase II study.

PATIENTS AND METHODS

Patient Selection

Patients with relapsed or refractory, histologically confirmed, indolent B-NHL, including small lymphocytic lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, splenic marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, nodal marginal zone B-cell lymphoma, and mantle cell lymphoma (MCL), according to the WHO classification[16] were eligible. Additional eligibility criteria included measurable disease; adequate hematologic (absolute neutrophil count $\geq$ 1,500/μL and platelet count $\geq$ 75,000/μL), renal (serum creatinine $<$ 1.5$\times$ the upper limit of normal [ULN]), and hepatic (AST and ALT $<$ 2.5$\times$ ULN and total bilirubin $<$ 1.5$\times$ ULN) function; an Eastern Cooperative Oncology Group performance status of 0 to 2[17]; age between 20 and 74 years; and expected survival of 3 months or longer. Patients with infection or serious complications or CNS disease or who had received purine analogs, such as fludarabine, cladribine, and pentostatin, were excluded. Other exclusion criteria included positivity for hepatitis B virus surface antigen, hepatitis C virus, or HIV antibody; other active malignancy; interstitial lung disease; and a history of autoimmune hemolytic anemia. Patients had to have been more than 4 weeks from the last chemotherapy or more than 3 months from the last rituximab treatment. The study protocol was approved by the institutional review board of each participating institution before the patients were enrolled onto the study. Also, all participants gave their informed consent before they entered the study.

Central Pathology Review

Unstained microscopic slides of lymphoma tissues obtained on initial biopsy and/or relapse were collected and stained with hematoxylin and eosin. In addition, immunohistochemical analyses were conducted using monoclonal antibodies (mAbs) including an anti-CD20 mAb (L26; DAKO, Glostrup, Denmark),[18] anti-CD3 mAb (PS1; Novocastra, Newcastle upon Tyne, United Kingdom), anti-CD5 mAb (4C7; Novocastra), anti-CD10 mAb (56C6; Novocastra), and anti-cyclin D1 polyclonal antibody (MBL Co Ltd, Nagoya, Japan). Preparations that were stained with hematoxylin and eosin and immunohistochemically treated were microscopically examined by three hematopathologists (Yo.M., S. Nak., and S.M.). The diagnosis by the central review committee was regarded as the final diagnosis in cases where there was a discrepancy between the diagnosis of an institution and the diagnosis of the committee.

Protocol Treatment

Patients were planned to receive fludarabine phosphate tablets orally once daily on days 1 through 5 every 28 days for three to six cycles. In the first cycle, fludarabine phosphate tablets were administered at 40 mg/m^2/d. Thereafter, the dose was determined according to the assessment criteria for starting subsequent treatment cycles (starting criteria) as listed in Table 1. If a patient did not fulfill the criteria, the protocol treatment was delayed by 1-week increments until recovery. If the treatment was delayed for more than 7 days, the dose was reduced to 30 mg/m^2/d for all subsequent cycles. If postponement lasted longer than 14 days, the protocol treatment was interrupted. Prophylactic use of sulfamethoxazole/trimethoprim and acyclovir was allowed but not mandatory, and granulocyte colony-stimulating factor was used if necessary.

Table 1. Assessment Criteria for Starting Subsequent Treatment Cycles

Neutrophil count $\geq$ 1,200/μL (if G-CSF was used, 7 days or greater recovery period from the G-CSF administration is required before assessment)
Platelet count $\geq$ 7.5 $\times$ 10^4/μL (if transfusion was given, 7 days or greater recovery period from the transfusion is required before assessment)
AST $<$ 2.5$\times$ ULN excluding abnormalities attributable to primary disease
ALT $<$ 2.5$\times$ ULN excluding abnormalities attributable to primary disease
Total bilirubin $<$ 1.5 $\times$ ULN
Serum creatinine $<$ 1.5 $\times$ ULN
No persistent nonhematologic toxicity of grade 3 or greater

Abbreviations: G-CSF, granulocyte colony-stimulating factor; ULN, upper limit of normal.

Patient Monitoring and Follow-Up

Patients were admitted during the first cycle, but from the second cycle, they could be treated as outpatients. The following evaluations were performed during the pretreatment screening period: vital signs, ECG, laboratory studies, bone marrow aspiration, and computed tomography (CT) imaging. During treatment, the patients were observed by physical examination, CBC counts, and serum chemistry every week. CT scan and bone marrow aspiration were performed 4 weeks after the start of the first, third, and sixth courses. The patients were observed until 12 weeks after completion of the protocol treatment or until the assessment of progressive disease (PD).

Data Analysis

Responses were assessed according to the International Workshop Criteria for NHL[19] as follows. Complete response (CR) required the complete disappearance of all lesions and radiologic or biologic abnormalities and the absence of new lesions. CR unconfirmed (CRu) described patients who met the criteria of CR but who had an indeterminate bone marrow assessment or a more than 75% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of all the measurable lesions but with a residual mass. Partial response (PR) was defined as a more than 50% decrease from baseline in the SPD of all the measured lesions, no increase in size of any other lesions, and no new lesions. Stable disease was defined as neither a 50% decrease nor a 50% increase in the SPD of the measured lesions, and PD was defined as the appearance of any new lesion or a more than 50% increase in the SPD from nadir. Confirmation of response by repeat measurement 28 or more days later was not required. In addition to the efficacy evaluation at each participating institute, an independent, third-party panel of three radiologists (T.T., S. Naw., and M.M.) carried out a central evaluation using the collected CT films. The primary efficacy variable was best ORR (the relative frequency of responders showing CR, CRu, or PR) in the indolent B-NHL except for MCL (IL) and MCL cohorts. Secondary efficacy parameters included the CR rate and time to treatment failure (TTF), which was defined as the time period from the date of enrollment to the date of the assessment of PD, the date of death as a result of any cause, or the date necessitating other antilymphoma treatment, whichever occurred earlier.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Follicular Lymphoma International Prognostic Index (FLIPI) scores were calculated by summing the number of risk factors (age $>$ 60 years, Ann Arbor stage III or IV, hemoglobin $<$ 12 g/dL, elevated lactate dehydrogenase, and $>$ four nodal areas).[20] The following three risk groups were defined: low (none or 1 risk factor), intermediate (two risk factors), and poor risk (three to five risk factors).

Statistical Methods

The efficacy was separately analyzed in the IL and MCL cohorts. Only the assessment of central evaluation was relevant for efficacy evaluations. For the IL cohort, the study was designed assuming the threshold ORR of 25% to

Table 2. Patient Baseline Clinical Characteristics

Characteristic	IL Cohort (n = 46) No. of Patients	%	MCL Cohort (n = 6) No. of Patients	%
Age, years				
Median	55.5		58.5	
Range	30-73		48-73	
Sex				
Male	21		4	
Female	25		2	
Histology				
Small lymphocytic lymphoma	1	2		
Follicular lymphoma	41	89		
Marginal zone B-cell lymphoma	1	2		
MCL			6	100
Low-grade B-NHL, NOS*	3	8		
Ann Arbor stage†				
I	4		0	
II	7		1	
III	14		0	
IV	17		5	
Indeterminate	4		0	
B symptom†	1	2	0	0
ECOG PS†				
0	36		5	
1	9		1	
2	1		0	
LDH†				
Normal	36		4	
Elevated	10		2	
Maximum tumor†				
< 5 cm	29		3	
≥ 5 cm	17		3	
International Prognostic Index†				
L	27		2	
LI	13		2	
HI	3		1	
H	1		1	
Indeterminate	2		0	
Follicular Lymphoma International Prognostic Index†				
L	25		NA	
I	13			
P	6			
Indeterminate	2			
Previous treatment				
Chemotherapy	45	98	6	100
Rituximab	37	80	4	67
Radiation	11	24	2‡	33
Auto-PBSCT	1	2	0	0
No. of prior chemotherapy regimens				
Median	3		2.5	
Range	1-8		1-3	
Responses to the last prior chemotherapy/immunotherapy				
Responder	27		3	
Nonresponder	11		2	
Unknown	8		1	

Abbreviations: IL, indolent B-cell non-Hodgkin's lymphoma excluding MCL; MCL, mantle cell lymphoma; B-NHL, B-cell non-Hodgkin's lymphoma; NOS, not otherwise specified; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; L, low risk; LI, low-intermediate risk; HI, high-intermediate risk; H, high risk; I, intermediate risk; P, poor risk; NA, not applicable; Auto-PBSCT, autologous peripheral-blood stem-cell transplantation.

*Confirmed as low-grade B-NHL, NOS, but the histologic subtype was indeterminate in the central pathology review.

†At the time of entry.

‡One patient received ibritumomab tiuxetan.

reliably detect an expected ORR of 45%. With the level of significance at 5% (one tailed), the required sample size to attain a statistical power of 80% was 36 patients. Assuming that up to 20% of the enrolled patients might be judged unassessable, the sample size was set at 45 patients. For the MCL cohort, the threshold ORR was set at 15%. It was designed to detect an expected ORR of 40%, with the level of significance at 5% (one tailed), and the required sample size to attain a statistical power of 70% was 14 patients. Therefore, considering a 20% possible exclusion rate, the sample size for the MCL cohort was initially set at 18 patients. However, because of slow accrual, we decided to prematurely close the recruitment for the MCL cohort.

RESULTS

Patient Characteristics

Between February 2003 and October 2003, 52 patients with relapsed or refractory indolent B-NHL were enrolled from 16 institutes. Forty-seven patients were enrolled onto the IL cohort, and five were enrolled onto the MCL cohort. In the central pathology review, one patient enrolled onto the IL cohort was found to have MCL. Therefore, the final number of patients belonging to each category was 46 in the IL cohort and six in the MCL cohort, as shown in Table 2. The central pathology review revealed that the IL cohort consisted mostly of follicular lymphoma patients (89%). The low number of MCL patients was primarily a result of the small population of MCL patients in Japan.[21] The majority of patients, 67% and 83% in the IL and MCL cohorts, respectively, had advanced-stage disease on entering the study. According to the International Prognostic Index,[22] 44 patients (85%) belonged to the low- or low-intermediate–risk group. When we applied the FLIPI[20] to the IL cohort, 25 patients (54%) were low risk, 13 patients (28%) were intermediate risk, and six patients (13%) were poor risk. All 52 patients had received chemotherapy except for one patient in the IL cohort who had received rituximab alone.

Protocol Treatment

In total, 243 cycles of the protocol treatment were delivered to the 52 patients, for a median of six cycles per patient (range, one to six cycles) and a mean of 4.7 cycles. The protocol treatment was discontinued in 10 patients before they completed the third cycle. The reasons for discontinuation were as follows: four patients developed PD, two developed adverse events (one patient had herpes zoster and one had interstitial lung disease), two withdrew their consent, and two did not meet the starting criteria. After the third cycle, 13 patients did not complete the planned six cycles of treatment. The reasons were as follows: four patients developed PD (one with herpes zoster), four had CRu judged as not requiring further therapy by the investigators, and seven did not meet the starting criteria (two with PD). Overall, 29 patients (56%) completed six cycles of the protocol treatment, whereas 11 patients (21%) were taken off study because of either adverse events or because they did not meet the starting criteria. According to the starting criteria, 12 patients (11 in the IL cohort and one in the MCL cohort) received reduced doses of 30 mg/m^2/d in subsequent treatment cycles. The reasons were as follows: seven patients had low neutrophil counts, one had a low platelet count, one had elevated bilirubin, and three had infections. Of these 12 patients, three eventually discontinued the treatment; two patients were in CRu and one patient discontinued treatment because of not meeting the starting criteria.

Efficacy

Table 3 lists the clinical responses to oral fludarabine. In the IL cohort, the ORR and CR rates were 65% (30 of 46 patients; 95% CI, 50% to 79%) and 30% (14 of 46 patients; 95% CI, 18% to 46%), respectively; and 23 (62%) of the 37 patients who had received prior rituximab responded to oral fludarabine. The MCL cohort consisted of six patients, of whom one achieved PR. The ORRs and CR rates correlated well with the risk groups according to the FLIPI. The median TTF for the 46 patients in the IL cohort was 8.6 months (95% CI, 6.6 to 12.0 months), and the median TTF for the 30 responders in the IL cohort was 12.0 months (95% CI, 8.6 months to not defined; Fig 1). The median TTF for the six patients in the MCL cohort was 6.1 months (95% CI, 4.6 to 8.7 months).

Adverse Events

Hematologic toxicities and nonhematologic adverse events are listed in Tables 4 and 5, respectively. Hematologic toxicity was the most frequently encountered toxicity. Grade 4 hematologic toxicities included neutropenia in 19 patients (37%). No patients developed grade 4 thrombocytopenia. Granulocyte colony-stimulating factor

Table 3. Antitumor Effect of Oral Fludarabine

Treatment Group	No. of Patients	No. of Patients					ORR		CR	
		CR	CRu	PR	SD	PD	%	95% CI	%	95% CI
IL	46	3	11	16	14	2	65	50 to 79	30	18 to 46
Rituximab (+)*	37	1	9	13	12	2	62		27	
Rituximab (−)*	9	2	2	3	2	0	78		44	
FLIPI										
Low	25	2	9	11	3	0	88		44	
Intermediate	13	1	2	3	6	1	46		23	
Poor	6	0	0	2	3	1	33		0	
MCL	6	0	0	1	5	0	17	0 to 64	0	0 to 46
Rituximab (+)*	4	0	0	1	3	0	25			
Rituximab (−)*	2	0	0	0	2	0	0			
Total	52	3	11	17	19	2	60	45 to 73	27	16 to 41

NOTE. Responses were assessed according to the International Workshop Response Criteria for Non-Hodgkin's Lymphoma.[19]
Abbreviations: ORR, overall response rate; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease; IL, indolent B-cell non-Hodgkin's lymphoma excluding MCL; FLIPI, Follicular Lymphoma International Prognostic Index; MCL, mantle cell lymphoma.
*Rituximab (+) and Rituximab (−) indicate the presence and absence of prior rituximab treatment, respectively.

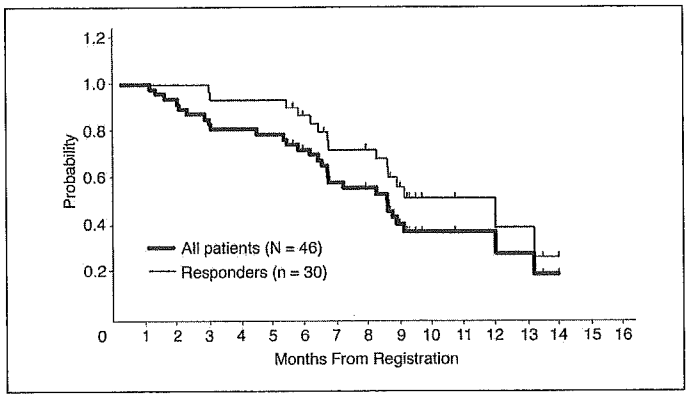

Fig 1. Estimated time to treatment failure (TTF) of patients with relapsed indolent B-cell non-Hodgkin's lymphoma (B-NHL) who received oral fludarabine phosphate. The median TTF for the 46 patients in the indolent B-NHL except mantle cell lymphoma (IL) cohort was 8.6 months (95% CI, 6.6 to 12.0 months), and the median TTF for the 30 responders in the IL cohort was 12.0 months (95% CI, 8.6 months to not defined).

was used in 40 (16%) of 243 cycles. Grade 3 infections occurred in 10 patients (19%) with 11 episodes, but neutropenic fever requiring admission occurred in only one patient. Two patients (4%) developed herpes zoster. They were not taking prophylactic acyclovir. One patient was found to have laryngeal cancer 1 month after completion of the sixth cycle of the protocol treatment and was treated with radiation.

Nausea/vomiting and diarrhea occurred in 50% and 37% of patients, respectively, but these toxicities were mostly of grade 1 or 2. All patients recovered with or without supportive treatment, and no patient required withdrawal from the study as a result of these toxicities. One patient developed grade 2 interstitial pneumonitis during the second cycle of treatment and recovered by treatment with high-dose glucocorticoid. The investigator assessed the relationship of this event as being possibly related to oral fludarabine.

Of 49 patients who received two or more cycles of the protocol treatment, 43 could receive the second and later cycles as outpatients. Two patients had prolonged initial hospitalization, one because of the occurrence of interstitial pneumonitis and the other as a precaution against infection. Four patients required admission as a result of adverse events (one patient each with pyelonephritis, bronchitis, pneumonia, and febrile neutropenia); all of the patients recovered.

After the follow-up period, two patients developed serious adverse events that were considered to be related to oral fludarabine. One patient developed grade 3 thrombocytopenia 1 year after completion of the sixth cycle of fludarabine treatment, when the platelet count decreased to $16 \times 10^3/\mu L$. Bone marrow examination revealed no dysplasia with a normal karyotype. The thrombocytopenia was improving but not recovered. One patient developed myelodysplastic syndrome (MDS) 7 months after receiving the fifth cycle of oral fludarabine. He showed PD to the fludarabine treatment and received rituximab and cyclophosphamide, vincristine, and prednisone thereafter. He developed anemia, and bone marrow examination revealed MDS with chromosome abnormalities. He received transfusions, but his MDS evolved into overt leukemia 6 months after diagnosis, and he died. The patient had been treated for follicular lymphoma for 20 years with multiple chemotherapy regimens including alkylating agents and radiation.

Two other deaths occurred after completing the study; one patient died as a result of PD, and the other patient died from a *Staphylococcal* infection after receiving subsequent chemotherapy. Both deaths were considered to be unrelated to oral fludarabine treatment.

DISCUSSION

This is the first study to document that oral fludarabine has an excellent efficacy profile against relapsed indolent B-NHL. For patients with indolent B-NHL except for MCL, the ORR was 65%, which is at least equivalent to the results for IV fludarabine monotherapy.[8-12,23] Also, the median TTF of 8.6 months was at least comparable to the TTF of 4.6 months for a similar population.[24] In a study using IV fludarabine in patients with relapsed indolent B-NHL, Klasa et al[12] reported an ORR of 64% and a progression-free survival time of 11 months, which is similar to this study. It was difficult to recruit MCL patients in this study, and the results for this population are not conclusive. Because the IV formulation is effective against MCL,[23,25-27] we assume that the oral formulation is also effective.

Hematologic toxicities were frequently encountered, but neutropenic fever requiring hospital admission occurred in only one patient, and no patients required a platelet transfusion. Presumably because of the oral formulation, relatively high incidences of GI toxicities were encountered, but most were mild and easily managed. In total, nonhematologic toxicities were mild.

According to the guideline for conducting clinical trials on anticancer agents in Japan, all 52 patients received the first cycle during admission. For 43 (88%) of the 49 patients who received two or more cycles, the second or later cycles were administered on an outpatient

Table 4. Incidence of Hematologic Toxicities of Grade 3 or Greater (N = 52)

	Any Grade		Grade 3		Grade 4	
Hematologic Toxicity	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukopenia	50	96	25	48	11	21
Lymphopenia	52	100	52	100	—	—
Neutropenia	51	98	17	33	19	37
Anemia	38	73	1	2	1	2
Thrombocytopenia	31	60	5	10	0	0

NOTE. Hematologic toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Table 5. Incidence of Nonhematologic Adverse Events of Grade 2 or Greater (N = 52)

Nonhematologic Adverse Event	Any Grade		Grade 2		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
LDH elevation	27	52	2	4	0	0	0	0
ALT elevation	22	42	3	6	0	0	0	0
ALP elevation	11	21	1	2	0	0	0	0
γ-GTP elevation	11	21	1	2	2	4	0	0
Bilirubin elevation	15	29	4	8	1	2	0	0
Constipation	14	27	10	19	1	2	0	0
Diarrhea	19	37	3	6	2	4	0	0
Nausea	26	50	4	8	1	2	0	0
Anorexia	22	42	4	8	0	0	0	0
Hematuria	17	33	1	2	1	2	0	0
Any infection*	27	52	8	15	10	19	0	0
Upper respiratory infection	16	31	4	8	3	6	0	0
Herpes zoster	4	8	2	4	2	4	0	0
Febrile neutropenia	2	4	0	0	2	4	0	0
Bronchitis	1	2	0	0	1	2	0	0
Pneumonia	1	2	0	0	1	2	0	0
Pyelonephritis	1	2	0	0	1	2	0	0
Other infection	6	12	2	4	1	2	0	0
Hypersensitivity	1	2	0	0	1	2	0	0
Headache	16	31	4	8	0	0	0	0
Rash	13	25	8	15	0	0	0	0
Fatigue	22	42	3	6	0	0	0	0
Insomnia	13	25	2	4	0	0	0	0
Supraventricular arrhythmia	2	4	1	2	1	2	0	0
Sinus tachycardia	2	4	0	0	1	2	0	0
Laryngeal cancer	1	2	0	0	0	0	1	2

NOTE. Nonhematologic adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.
Abbreviations: LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase.
*Indicates the number of patients who developed any infection as the greatest severity.

basis. The low admission requirement indicates that oral fludarabine is suitable for outpatients.

Two cases of malignancy occurred after completion of the fludarabine treatment. One patient who developed laryngeal cancer had complained of a sore throat, and we considered it to have no relationship with fludarabine. The patient who developed MDS after fludarabine treatment had a long disease course with multiple chemotherapies and radiotherapy, which may have contributed to the development of secondary MDS. In a review by Cheson et al,[28] patients with chronic lymphocytic leukemia or hairy cell leukemia who are treated with purine analogs have a higher incidence of secondary malignancy than expected according to the Surveillance, Epidemiology, and End Results 5-year age- and sex-specific incidence rates for the accumulated person-years at risk. However, these values are consistent with the increase that is already associated with these diseases. Although these two cases of malignancy are not considered to be related to the fludarabine treatment, patients who have a long course of disease or history of multiple chemotherapies need to be closely monitored for the development of second malignancy.

The high efficacy and low toxicity profiles of oral fludarabine for patients with relapsed indolent B-NHL in the present study and the reported favorable results of several phase II studies on combination chemotherapy containing IV fludarabine[23,29,30] suggest that oral fludarabine might be a promising agent in combination with other antilymphoma agents including rituximab. In addition to the definitive role as a useful palliative monotherapy for patients with relapsed indolent B-NHL, oral fludarabine is expected to show efficacy in combination therapy for relapsed and untreated patients, warranting further investigations.

In conclusion, oral fludarabine phosphate is highly effective for patients with relapsed indolent B-NHL who have mostly been pretreated with rituximab and is more convenient than the IV formulation. Further investigations including combination with other antilymphoma agents are warranted.

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Appendix

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The authors indicated no potential conflicts of interest.