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Appendix

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®).

Glossary Terms

Dipeptidyl peptidase IV (DPP4): A cell membrane serine exopeptidase that cleaves dipeptides from the N terminus of proteins. DPP4 is involved in the metabolic inactivation of glucagon-like peptide-1 (GLP1).

Hierarchical clustering: An analytical tool used to find the closest associations among gene profiles and specimens under evaluation.

c-kit: A member of the PDGFR family, c-kit is a tyrosine kinase receptor that dimerizes following ligand binding and is autophosphorylated on intracellular tyrosine residues.

PDGFRA (platelet-derived growth factor alpha): The receptor for PDGF exists distinctly as the dimeric $\alpha\alpha$ or $\beta\beta$ form. All dimer combinations of PDGF A and B signal through PDGFR-$\alpha\alpha$; PDGF BB signals through PDGFR-$\beta\beta$; PDGF CC signals through the $\alpha\alpha$ and $\alpha\beta$ receptors; and PDGF DD signals through the $\beta\beta$ and $\alpha\beta$ receptors.

Ki67: A marker of proliferation, Ki67 is a protein that is expressed in the nucleus of proliferating cells. Absent only in resting cells, cells in the G1, S, G2, and M phase of the cell cycle express this marker.

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論　策

わが国の小児造血器腫瘍診療施設の実態

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京都大学大学院小児発達医学[4]，日本小児白血病リンパ腫研究グループ[5]
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要　旨

小児造血器腫瘍の標準的治療法の確立と質の高い臨床試験を行うために2003年にわが国の全ての小児白血病研究グループが結集して日本小児白血病リンパ腫研究グループ（JPLSG）が設立された．この結果，わが国のほぼ全ての小児造血器腫瘍診療施設がJPLSGに参加していると考えられる．今回，JPLSG参加施設の基本情報把握のため施設調査を行い，わが国の小児造血器腫瘍の診療実態と今後の研究基盤および診療体制の整備について検討した．方法は，調査票を郵送にて送付回収した．回収率は100％で186施設について検討した．主な結果は，都道府県別の施設数は，2施設以下27県，10施設以上3都府県，小児血液腫瘍担当医師数が2名以下96施設，施設責任者もしくは実務担当者が血液専門医でない施設78施設，小児外科腫瘍を診療している施設108施設，2005年度に造血幹細胞移植を実施した施設111施設，小児血液専任のデータ管理者がいる施設10施設．小児造血器腫瘍の診療は，少ないスタッフで固形腫瘍や移植医療とともに行われている実態が明らかとなった．施設間格差はまだ大きく，大都市圏での施設の集約化，地方施設の診療スタッフ確保，さらに専門医療の教育研修システムの構築が急がれる．また，臨床試験を円滑に行うには意識改革とともにスタッフの負担軽減に繋がる支援体制の強化が必要と思われた．

キーワード：小児造血器腫瘍，小児白血病，診療体制

はじめに

急性リンパ性白血病をはじめとする小児造血器腫瘍は，化学療法，支持療法，造血幹細胞移植療法，さらには診断技術の向上に基づいたリスク層別法の発達により80％以上の長期生存が可能となってきた[1]．これらの治療法の多くは欧米の研究グループで行われた臨床試験によって開発されたが，我が国でも1970年代から自主的に組織された治療研究グループによって治療研究が推進され，小児造血器腫瘍のほとんどの症例がいずれかの研究グループの治療法で治療されてきた．現在では，小児癌白血病研究グループ（CCLSG），小児白血病研究会（JACLS），九州山口小児がん研究グループ（KYCCSG），東京小児がん研究グループ（TCCSG）の4つの研究グループに集約されており，ALLの治療研究が独自に行われている[2]．一方，稀少な難治性疾患については，単一グループでは十分な症例数が得られないため治療開発が困難であったことから90年代になって厚生省研究班による全国規模の多施設共同研究が推進され，乳児白血病，急性骨髄性白血病の治療法開発が行われてきた[3)4)]．しかし，これまでは各研究グループおよび参加施設が臨床試験としての認識に乏しかったため，治療研究は倫理審査が行われないまま簡素な治療計画書のみによって行われ，研究的治療も症例登録基準があいまいなこと，治療変更が各施設の自由裁量であったこと，症例報告書の提出・内容確認が不十分なこと，有害事象の報告義務がないことなど，必ずしも質の高い研究体制の下で行われていたとはいえなかった．そこで，臨床研究基盤整備と質の高い臨床試験の推進のために2002年に小児造血器腫瘍の標準的治療法の確立のための研究班がスタートした[2]．これを期に，2003年に我が国のすべての小児白血病研究グループが結集して日本小児白血病リンパ腫研究グループ（JPLSG）が設立され，グループ間共同研究として全国共同治療研究が開始された．これまでにJPLSGとして10の臨床試験が開始されており，乳児ALL，非ホジキンリンパ腫，急性骨髄性白血病（AML）は，全国統一の治療研究が行われている[5]．その結果，すべての患者さんに同じ治療法，臨床試験を受ける機会が与えられるようになった．

がん治療は，毒性の強い治療法を組み合わせて行うことから，専門的知識と経験が要求される．本来は，

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表1 JPLSG参加施設の施設母体

		CCLSG	JACLS	KYCCSG	TCCSG
大学病院：	91 施設	13	36	6	36
小児病院：	15 施設	2	6	0	7
がんセンター	4 施設	3	0	1	0
国公立総合病院 (NHOを含む)	41 施設	6	28	3	4
日赤病院	15 施設	1	12	0	2
その他	20 施設	2	14	1	3
合計	186 施設	27	96	11	52

CCLSG：小児癌白血病研究グループ，JACLS：小児白血病研究会，KYCCSG：九州山口小児がん研究グループ，TCCSG：東京小児がん研究グループ，NHO：国立病院機構

表2 都道府県別参加施設数

施設数	1	2	3	4	6	7	8	9	>10
都道府県数	9	18	8	1	2	2	2	2	3

>10：14，17，22施設

小児がん専門医が当たるべきであるが，我が国には専門医制度は未だ確立されておらず，個々の医師・医療機関の経験をもとに診療が行われている．小児がんは稀少な病型が多いため，多くの病型に十分な診療経験を持った医師の育成には，短期間に多数例を経験できる施設が必要である．また，ほとんどの症例が臨床研究に参加して治療されることから，診療施設は，臨床試験を実施しうる体制が求められる．JPLSGでは，質の高い医療と臨床試験を担保するために，以下の施設基準を設けている．(1)日本小児血液学会会員がいる，(2)包括医療ができる小児がん治療チームがある，(3)機関審査委員会(IRB)または倫理審査委員会がある，(4)施設監査が受け入れられる．また，わが国のほぼ全ての小児造血器腫瘍診療施設がJPLSGに参加していると考えられることから，JPLSG参加施設が我が国の小児血液がんの診療の担い手であるともいえる．今回，施設の基本情報の把握のために行ったJPLSG参加施設の調査結果をもとにわが国の小児造血器腫瘍の診療実態と今後の研究基盤および診療体制の整備について検討したので報告する．

方　法

平成18年7月1日時点のJPLSG参加施設の187施設に調査票を郵送して回収し集計した．調査票の回収率は100%(一部未記入を含む)であった．今回，その後に退会した1施設を除いた186施設（表8参照）について検討した．グループ別施設数の内訳は，CCLSG 27施設，JACLS 96施設，TCCSG 52施設，KYCCSG 11施設であった．

調査票にある項目は，以下の通りである．施設研究責任者氏名，実務担当者氏名，施設病床数，小児科病床数，小児血液腫瘍病床数，病棟形態，専門医研修施設認定状況，後期研修受け入れ状況，小児科常勤医数，小児血液腫瘍担当医数，学会入会・専門医取得状況，放射線治療医・小児外科医・麻酔科医の有無，診療対象腫瘍性疾患分類，メソトレキサート(MTX)血中濃度測定・全身放射線照射・無菌室管理の可否，造血幹細胞移植実施件数，病名告知実施状況，患者支援設備・スタッフの有無，研究審査状況，研究支援体制の有無．

結　果

参加施設の組織母体の内訳をグループ別に示す（表1）．大学病院の占める割合が37.5%～69.2%と較差が見られ，グループ間で施設背景に差異がみられた．また，都道府県別の参加施設数は，1～2施設の県が27施設と過半数を占めたが，大都市圏(8都府県)では，14～22施設と多かった(表2)．施設病床数は500床以上の大病院が80%を占めた(図1a)．小児科病床数も30床以上の施設が70%以上を占めた(図1b)，そのうち小児科単独病棟を持つ施設は105施設で，81施設は混合病棟であった．小児血液腫瘍病床数は，6床以上確保されている施設は35%に過ぎず，約半数は不定の回答であった(図1c)．専門医研修施設認定状況は，日本小児科学会専門医研修施設が174施設（93.5%），日本血液学会専門医研修施設が154施設（82.8%）であった．

小児科医師数については，小児科常勤医師数が10名以上の施設が60%を占めるものの，4名以下の施設が32施設あった(図2a)．また，小児血液腫瘍を担当する医師数は2名以下が96施設と過半数を占めた(図

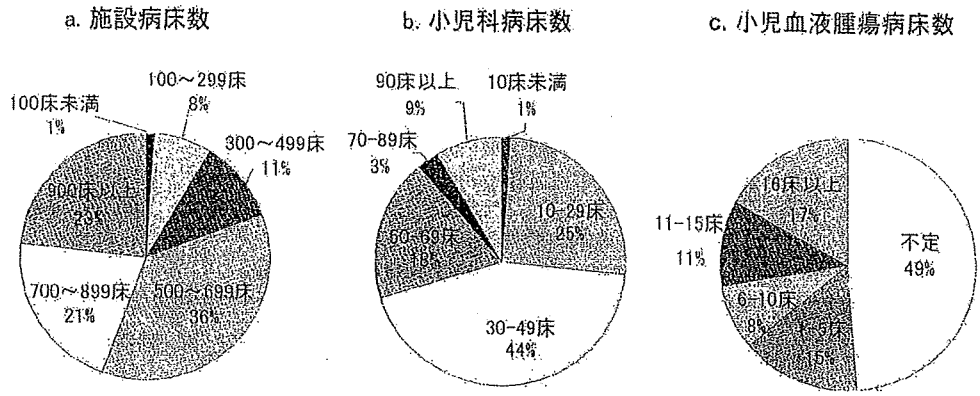

図1　施設規模

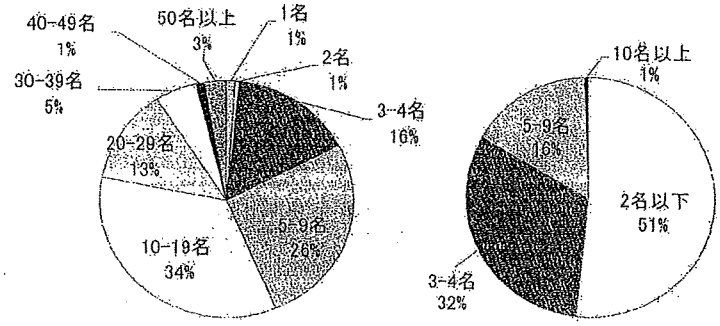

図2　医師数

表3　施設責任者もしくは実務担当者の学会入会・専門医取得状況

(施設数)	有	無
日本小児血液学会会員	185	1
日本小児がん学会会員	153	15
日本血液学会会員	156	14
小児科専門医	179	7
日本血液学会血液専門医	100	78

2b)．医師のうち，施設研究責任者もしくは実務担当者の学会入会・専門医取得状況を調査したところ，いずれもが日本小児血液学会会員でない施設が1施設，いずれもが小児科専門医でない施設が7施設，いずれもが血液専門医でない施設が78施設であった(表3)．また，関連診療科として放射線治療医，小児外科医，麻酔医の有無について尋ねたところ，それぞれ8施設，37施設，1施設で常勤または非常勤医師いずれもが不在であった（表4)．

小児がんの診療分野としては，造血器腫瘍のほか，小児外科腫瘍が108施設（58.1%)，眼腫瘍が50施設(26.9%)，骨軟部腫瘍が80施設(43.0%)，脳腫瘍が88施設（47.3%）で診療されていた．MTX血中濃度測定

表4　放射線治療医・小児外科医・麻酔科医の有無

	常勤	非常勤	無し
放射線治療医	158施設	19施設	8施設
小児外科医	134施設	15施設	37施設
麻酔科医	183施設	2施設	1施設

が自施設で可能な施設は136施設(73.1%)に留まっていた．

造血幹細胞移植のための設備と実施状況は，無菌室が159施設（85.5%)，全身放射線照射装置は145施設(87.0%)で設置されており，2005年度においては，111施設(59.7%)で自家移植，血縁移植，非血縁骨髄移植，臍帯血移植のいずれかが実施されていた（表5)．

患者支援設備・スタッフについては，145施設(78.0%)に院内学級が設置されていたが，患者支援の設備やスタッフは，26.9～46.2%に留まっていた(表6)．

IRBまたは倫理審査委員会の設置は，IRBは175施設(94.1%)に，倫理審査委員会は2施設を除くすべての施設に設置されていた．しかし，プロトコールの倫理審査実施については，常にと回答した施設は154施設(82.8%)に留まり，時に回答した施設が4施設認められた．また，小児血液腫瘍専任のデータマネジャー

表5　2005年度造血幹細胞移植実施状況

		同種			移植の実施
	自家	血縁*	非血縁	臍帯血	
有	82施設	80施設	52施設	49施設	111施設
無	104施設	106施設	134施設	137施設	75施設

表6　患者支援設備・スタッフの有無

	院内学級	家族用宿泊施設	患者支援ボランティアグループ	親の会	保育士・CLS	小児心理士
有	145施設	50施設	67施設	60施設	77施設	86施設
無	41施設	136施設	119施設	126施設	100施設	91施設

CLS：Child Life Specialist

表7　主要国の小児造血器腫瘍診療施設規模の比較

国名		日本	アメリカ合衆国	ドイツ	フランス	イギリス
小児人口（0～14歳）（統計年）[10]		1,752万人（2005年）	6,076万人（2004年）	1,204万人（2004年）	1,116万人（2003年）	1,089万人（2004年）
施設数（グループ，調査年）		186（JPLSG，1997～2001）[5]	231（COG，2003～2005）[6]	92（GPOH，2002～2006）[7]	33（SFCE，2006）[8]	22（MRC-CLWP，-）[9]
年間臨床試験登録数（ただし，ドイツとイギリスは年間疾患登録数）別施設数	集計対象疾患	造血器腫瘍	造血器腫瘍＋固形腫瘍	造血器腫瘍＋固形腫瘍	造血器腫瘍＋固形腫瘍	造血器腫瘍＋固形腫瘍
	登録数 50～	0	9	9	8	22
	登録数 40～49	0	6	6	3	0
	登録数 30～39	0	16	6	8	0
	登録数 20～29	2	28	12	7	0
	登録数 10～19	11	61	19	5	0
	登録数 5～9	64	68	11	1	0
	登録数 1～4	90	37	19	1	0
	登録数 ≦1	19	6	10	0	0
年間登録数20例以上の施設（JPLSGは10例以上）で占める登録数の割合		21%	58%	77%	94%	100%

JPLSG：Japanese Pediatric Leukemia/Lymphoma Study Group，COG：Children's Oncology Group，GPOH：Gesellschaft für Pädiatrische Onkologie und Hämatologie，SFCE：La Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent，MRC-CLWP：Medical Research Council-Childhood Leukemia Working Party

のいる施設はわずか10施設（5.4%）であった．

考　察

日本小児白血病リンパ腫研究グループ（JPLSG）参加施設の実態調査結果を報告した．わが国の小児造血器腫瘍診療施設のほとんどがJPLSGに参加していることから，今回の調査結果は，我が国の小児血液腫瘍の診療の実態を表している．参加施設の多くが日本小児科学会専門医研修施設かつ日本血液学会専門医研修施設であることから，教育機能のある施設で小児血液腫瘍の診療が行われているといえる一方で，参加施設の過半数が，少数の入院患者を2名以下の専門スタッフで診療している実態がうかがわれた．これは，厚生労働省研究班で調査された5年間の小児白血病リンパ腫の臨床研究登録数を調査した際に年間登録数が10例以上の施設はわずか16施設にすぎず，過半数が年間登録数2例以下の施設であったことと合致する結果である[5]．欧米では，造血器腫瘍を始め，稀少で濃厚な治療を要する小児がんの診療は，主に大規模診療施設で治療されている．実際，イギリス[9]，フランス[8]，ドイツ[7]，アメリカ[6]では，それぞれ100%，94%，77%，58%の患者が年間20例以上の小児がん登録数のある施設で診療されている（表7）．とりわけ，イギリスでは，小児がん診療センターが22施設しかなく，施設条件として4～5名のコンサルタントと血液分野と固形分野に精通したい医師がそれぞれ2名以上いる体制で年間80例以上の新患を診療することが推奨されている[9]．一方，わが国では，白血病リンパ腫の年間登録数が10

表8　JPLSG参加施設一覧　2007.3.31現在

CCLSG
- 国立病院機構北海道がんセンター
- 中通総合病院
- 新潟大学医歯学総合病院
- 新潟県立がんセンター新潟病院
- 福島県立医科大学附属病院
- 日本大学医学部附属板橋病院
- 国立国際医療センター
- 静岡県立静岡がんセンター
- 静岡県立こども病院
- 愛知医科大学病院
- 金沢大学医学部附属病院
- 富山大学医学部附属病院
- 富山市民病院
- 金沢医科大学附属病院
- 滋賀医科大学附属病院
- 大阪医科大学
- 鳥取大学医学部附属病院
- 国立病院機構香川小児病院
- 徳島大学医学部附属病院
- 長崎大学医学部・歯学部附属病院
- 秋田大学医学部附属病院
- 市立秋田総合病院
- 大阪労災病院
- 鳥取県立中央病院
- 石川県立中央病院
- 高知赤十字病院
- 沖縄県立南部医療センター

JACLS
- 旭川赤十字病院
- 札幌医科大学附属病院
- 北海道大学医学部附属病院
- KKR札幌医療センター
- 旭川医科大学附属病院
- 北海道立小児総合保健センター
- 市立函館病院
- 特定医療法人北楡会札幌北楡病院
- 浜松医科大学附属病院
- 聖隷浜松病院
- 豊橋市民病院
- 安城更生病院
- 藤田保健衛生大学附属病院
- 名古屋市立大学医学部附属病院
- 名古屋大学医学部附属病院
- 名古屋第一赤十字病院
- 名古屋第二赤十字病院
- 国立病院機構名古屋医療センター
- 一宮市立市民病院
- 小牧市民病院
- 岐阜大学医学部附属病院
- 岐阜市民病院
- 三重大学医学部附属病院
- 県西部浜松医療センター
- 岡崎市民病院
- 名鉄病院
- 名古屋市立東市民病院
- 奈良県立医科大学附属病院
- 関西医科大学附属枚方病院
- 大阪大学医学部附属病院
- 大阪市立総合医療センター
- 大阪赤十字病院
- 国立病院機構大阪医療センター
- 大阪府立急性期・総合医療センター

JACLS
- 大阪府立母子保健総合医療センター
- 近畿大学医学部附属病院
- 和歌山県立医科大学附属病院
- 兵庫医科大学附属病院
- 神戸大学医学部附属病院
- 兵庫県立こども病院
- 大阪市立大学医学部附属病院
- 中野こども病院
- 市立吹田市民病院
- 姫路赤十字病院
- 近畿大学医学部附属堺病院
- 川崎医科大学附属病院
- 岡山大学医学部・歯学部附属病院
- 国立病院機構岡山医療センター
- 岡山赤十字病院
- 岡山済生会総合病院
- 倉敷中央病院
- 広島大学医学部附属病院
- 広島赤十字・原爆病院
- 国立病院機構呉医療センター
- 香川大学医学部附属病院
- 高知大学医学部附属病院
- 高知医療センター
- 愛媛大学医学部附属病院
- 松山赤十字病院
- 愛媛県立中央病院
- 島根大学医学部附属病院
- 大分大学医学部附属病院
- 佐賀大学医学部附属病院
- 産業医科大学附属病院
- 北九州市立八幡病院
- 琉球大学医学部附属病院
- 京都大学医学部附属病院
- 国立病院機構京都医療センター
- 京都桂病院
- 神戸市立中央市民病院
- 西神戸医療センター
- 天理よろづ相談所病院
- 日本赤十字和歌山医療センター
- 滋賀県立小児保健医療センター
- 大津赤十字病院
- 島根県立中央病院
- 松江赤十字病院
- 福井大学医学部附属病院
- 市立岸和田市民病院
- 市立島田市民病院
- 財団法人田附興風会北野病院
- 国立病院機構舞鶴医療センター
- 京都第一赤十字病院
- 京都市立病院
- 明石市立市民病院
- 松下記念病院
- 社会保険神戸中央病院
- 京都府立医科大学附属病院
- 弘前大学医学部附属病院
- 青森県立中央病院
- 岩手医科大学附属病院
- 岩手県立北上病院
- 東北大学病院
- 山形大学医学部附属病院
- いわき市立総合磐城共立病院
- 宮城県立こども病院

KYCCSG
- 国立病院機構九州がんセンター
- 九州大学病院
- 大分県立病院
- 浜の町病院
- 福岡大学病院
- 久留米大学医学部附属病院
- 鹿児島市立病院
- 山口大学医学部附属病院
- 宮崎大学医学部附属病院
- 北九州市立医療センター
- 鹿児島大学病院

TCCSG
- 茨城県立こども病院
- 神奈川県立こども医療センター
- 熊本大学医学部附属病院
- 群馬大学医学部附属病院
- 慶應義塾大学病院
- 国立病院機構熊本医療センター
- 国立成育医療センター
- 埼玉医科大学病院
- 埼玉県立小児医療センター
- 東京慈恵会医科大学附属病院
- 自治医科大学附属病院
- 順天堂大学医学部附属順天堂病院
- 昭和大学藤が丘病院
- 信州大学医学部附属病院
- 聖マリアンナ医科大学附属病院
- 聖路加国際病院
- 千葉大学医学部附属病院
- 千葉県こども病院
- 帝京大学医学部附属病院
- 東海大学医学部附属病院
- 東京医科歯科大学附属病院
- 東京医科大学附属病院
- 東京大学医学部附属病院
- 東京女子医科大学東医療センター
- 東邦大学医療センター大森病院
- 獨協医科大学附属病院
- 都立清瀬小児病院
- 都立駒込病院
- 日本医科大学附属病院
- 山梨大学医学部附属病院
- 横浜市立大学医学部附属病院
- 東京大学医科学研究所
- 北里大学医学部附属病院
- 筑波大学附属病院
- 群馬県立小児医療センター
- 杏林大学医学部付属病院
- 長野県立こども病院
- 東京慈恵会医科大学柏病院
- 東京慈恵会医科大学附属第三病院
- 成田赤十字病院
- 松戸市立病院
- 帝京大学ちば総合医療センター
- 東京歯科大学市川総合病院
- 足利赤十字病院
- 東邦大学医療センター大橋病院
- 埼玉医科大学総合医療センター
- 聖マリアンナ医科大学横浜市西部病院
- 帝京大学医学部附属溝口病院
- 昭和大学病院
- 済生会横浜市南部病院
- 東京西徳洲会病院
- 防衛医科大学校附属病院

例以上の施設において全体のわずか21.4%を診療しているに過ぎず[2]，如何に小規模診療施設に依存した診療体制にあるかがわかる．さらに，参加施設の60%近い施設が同じスタッフで固形腫瘍の診療や移植医療も行っており，欧米ではすでに分業化が確立した診療分野を，わが国では少ないスタッフで手広く診療している実態が浮き彫りとなった．また，都道府県別では，2施設以下が27県あるものの，6～9施設が8道府県あり，3都府県では，参加施設数がそれぞれ，22，17，14と多い．年間900例足らずの小児造血器腫瘍の新規患者に対してこれら186施設で診療が行われているが，診療体制の格差が大きく，また，専門性の高い施設が限られている．専門医の育成のためには短期で十分な診療経験を持たせる必要があることからも診療規模の大きな施設が求められる．とりわけ，大都市圏では，症例の集約化とそれを受け入れる施設の整備とマンパワーの確保（集約化）が必要である．一方，症例の少ない地方地域では，診療スタッフの確保が重要課題であるとともにセンター病院とサテライト病院の連携システムを構築して患者の利便性に配慮した診療システムの構築が望ましいと思われる．

施設責任者もしくは実務担当者自身が小児科専門医でない施設が7施設，血液専門医でない施設は78施設に及ぶ．小児造血器腫瘍の臨床試験を行うJPLSGの参加施設として医療の質の確保するためには，小児がん専門医制度がない現段階では，血液専門医の存在が小児血液疾患診療の質の担保の目安と考えられる．JPLSGでは，2年後を目途に参加施設基準に血液専門医がいることを加える予定である．

臨床試験の実施の条件としてプロトコールの倫理審査は必須であるが，未だプロトコールの倫理審査の完全実施率は82.8%に留まっていた．臨床研究に対する倫理的配慮の意識の一層の徹底が必要である．また，診療現場で臨床試験をサポートするスタッフを置いている施設はわずか10施設であり，今後，臨床研究の質の確保と医師の負担軽減のためには施設への支援の充実が必要であろう．さらに，多くの施設が同一スタッフで固形腫瘍の診療も行っていることから臨床研究基盤の共有化が効率的で，かつ施設負担の軽減に繋がるかもしれない．

小児造血器腫瘍の医療の質の確保には療養環境の整備も不可欠である．78%の施設に院内学級が設置されているものの，患者支援の設備やスタッフは，50%未満に留まっており，トータルケアの充実も求められる．

結　語

小児造血器腫瘍の診療は，固形腫瘍や造血幹細胞移植など欧米ではすでに分業化が確立した診療分野と合わせて少ないスタッフで診療が行われている実態が明らかとなった．施設間格差は未だ大きく，大都市圏での施設の集約化，地方施設の診療スタッフ確保，および専門医療の教育研修システムの構築が急がれる．また，このような状況下で臨床試験を円滑に行うには意識改革とともにスタッフの負担軽減に繋がる支援体制の強化が必要と思われた．

謝辞　調査にご協力いただいたJPLSG参加施設（表8）の方々に深謝します．なお，本論文の内容は第110回日本小児科学会学術集会（京都）にて発表した．また，本研究は，厚生労働科学研究費補助金（がん臨床研究事業）「小児造血器腫瘍の標準的治療法の確立に関する研究」の一部として行われた．

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The Realities of the Medical System for Pediatric Hematologic Malignancies in Japan

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Gathering all of the pediatric leukemia groups in Japan, the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) was organized to undertake high quality clinical trials to establish the standard therapy for pediatric hematologic malignancies in 2003. In this study, the realities of the medical system for pediatric hematologic malignancies in Japan were revealed by the questionnaire to the hospitals participating in JPLSG. Replies were obtained from all 186 hospitals and were analyzed. There were 96 hospitals with less than 3 staff, 78 hospitals with no staff on the hematologic board, 108 and 111 hospitals with clinical service for solid tumors and hematopoietic stem cell transplantation (HSCT), respectively. A clinical research coordinator working for pediatric malignancies was found only in 10 hospitals. The study revealed that clinical services for hematologic malignancies, solid tumors and HSCT were all provided by the small number of staff, and that the service quality varied among the hospitals. In conclusion, intensified service systems in metropolitan areas, the securing of staff in local areas, and on education system for raising specialists will be needed in the near future. Supporting system for local staff to relieve the burden will be also required to carry out high quality clinical trials.

Pediatr Blood Cancer 2009;52:591–595

Retrospective Analysis of Relapsed or Primary Refractory Childhood Lymphoblastic Lymphoma in Japan

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Background and Procedure. To assess the clinical course with response to second-line treatment and to evaluate the role of hematopoietic stem cell transplantation (SCT) in children with relapsed or primary refractory lymphoblastic lymphoma (LBL), we analyzed data of 48 patients with relapsed/primary refractory diseases among 260 LBL patients identified in a national survey of 1996–2004. ***Results.*** Twenty-six patients achieved second complete remission; 9 achieved partial remission. Of 13 patients who showed progression despite first and second line therapy, only one patient was alive on the second relapse after unrelated cord blood transplantation. Among 40 relapsed patients, the median time between initial diagnosis and relapse was 12.5 months (range 3–56 months). The sites of relapse were isolated BM (n = 9), primary local site with BM (9), primary local site (6), isolated CNS (4), local site with mediastinum (4), primary local site with other site (4), and others (4). Of all 48 patients, 3 were alive after chemotherapy alone. Of the 33 patients, 14 were alive after high dose chemotherapy (HDC)/SCT. With a 27.5-month median follow up period, the 3-year OS rate was 43.2 ± 7.4% (estimate ± SE). Univariate analysis identified two features (relapse within 12 months, T cell phenotype) as significant variables that predicted poor survival. Multivariate analysis showed novel statistically significant variables including relapse within 12 months from initial diagnosis (Hazard ratio 3.60) and absence of HDC/SCT (2.64). ***Conclusion.*** Outcomes of patients with relapsed/primary refractory LBL were poor, but HDC/SCT for these patients was associated with good results. Pediatr Blood Cancer 2009;52:591–595. © 2009 Wiley-Liss, Inc.

Key words: children; lymphoblastic lymphoma; recurrence; refractory

INTRODUCTION

Malignant lymphoma is the fourth most frequent of all Japanese childhood cancers. It represents 5% of all new cases. Lymphoblastic lymphoma (LBL) is a major histology of childhood NHL, accounting for about 30%. Excellent outcomes for children with LBL have been reported with protocols closely modeled on therapy designed for acute lymphoblastic leukemia (ALL) [1]. However, 20–40% of patients develop relapse or primary refractory disease. They have poor prognoses [2,3]. The clinical courses and outcomes of these relapsed or primary refractory LBL of children have not been well documented [2,4].

To determine the response to second-line treatment and the outcomes of children with a relapsed or primary refractory LBL and to evaluate the role of high dose chemotherapy and stem cell transplantation (HDC/SCT) in these patients, we performed a retrospective nationwide analysis of LBL patients in Japan.

PATIENTS AND METHODS

Among 260 patients with LBL registered in a national survey during 1996–2004, 48 patients (18.5%) from 39 institutions with primary refractory or relapsed diseases were found, including 8 primary refractory diseases and 40 relapses. Their medical records were reviewed. Relapse was defined as appearance of new lesions, re-growth of original masses and obvious enlargement of the mediastinal mass as revealed by imaging study with pathological examination in principle, and appearance of tumor cells in bone marrow and cerebrospinal fluid. Among 40 relapsed patients, 25 were confirmed relapse by histological/cytological examinations, 9 were defined with only clinical courses and imaging studies, and the rest of 6 were unknown about precise information. Among five patients recurred with mediastinal masses, four were confirmed by histological/cytological study, and one was determined by only imaging studies. Clinical data including treatment and follow-up information were gathered from a review of relapsed or primary refractory patient charts through the Japanese Pediatric Leukemia Lymphoma Study Group (JPLSG). The JPLSG comprises four children's hematology/oncology study groups: Japan Association of Childhood Leukemia Study, Tokyo Children's Cancer Study Group, Japan Children's Cancer and Leukemia Study Group, and Kyushu-Yamaguchi Children's Cancer Study Group. First line treatments differed among groups. The most frequently used treatment regimens were based on the framework of the LSA2-L2 protocol or the BFM group strategy [5,6]. After 4–6 weeks of ALL-therapy-like induction, some courses of consolidation and intensification were done for first line therapy followed by maintenance consisting of multi-agent block therapy or oral 6-MP with weekly MTX. Actual drugs and dose during consolidation, intensification and maintenance varied among groups. Total durations of therapy were of two types: 18 and 24 months.

Second line treatment also varied. Among 41 patients for whom descriptions of second line chemotherapy regimen were available, 11 received their own first line protocol similar to high risk ALL

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induction, 12 received therapy of other high risk ALL induction, 5 received AML type therapy, 3 underwent an ifosfamide, carboplatin, etoposide (ICE) [7] regimen, 6 received myeloablative stem cell transplantation as a re-induction therapy, and 4 received other therapies. Because of the lack of uniformity in the therapeutic regimens for refractory or recurrent cases, we mainly examined these patients' characteristics with the prognostic significance of the variables on overall survival.

Using Kaplan–Meier estimates, curves were calculated for the probability of overall survival together with standard error (SE). Univariate analyses of the association of various clinical factors were done with overall survival. The curves were compared using a double-sided log rank test. $P < 0.05$ at both sides was considered significant. The overall survival (OS) rate was calculated from the time of initial diagnosis to death. Progression free survival (PFS) was calculated from the time of relapse or refractory phase to disease progression. Multivariate analyses were performed using the Cox proportional-hazard model. Variables with P-values ≤ 0.1 in prior univariate testing were included.

RESULTS

Table I portrays representative characteristics of primary refractory or relapsed patients. Male patients were 66.7%, which is similar to the 70% males among all NHL patients. Of the patients, 81% showed greater than clinical stage III at initial diagnosis. Among 48 patients, 2 eventually revealed an NK type immunophenotype after initiation of first line LBL type therapy. Both achieved complete remission (CR) with first line therapy, but recurred. One was refractory to second line therapy; the patient received unrelated cord blood transplantation (UCBSCT) and died of graft failure. Another patient achieved partial remission (PR) with second line therapy, received allogeneic bone marrow transplantation (BMT), and entered into continuous CR.

Sites of relapse were the primary local site (12.5%), and the primary site with another site (35.4%) (Table II). Of 40 relapsed patients, 33 exhibited recurrence during first line chemotherapy and 7 after it (3–56 months after diagnosis, median 12.5 months). The patients' clinical courses and outcomes are shown in Figures 1 and 2. Of all primary refractory/relapsed patients, 26 patients achieved CR; and 9 patients achieved PR after second line chemotherapy. Among 13 patients who progressed in spite of first and second line chemotherapy, 1 patient was alive at the analysis on second relapse after UCBSCT, 8 patients died of therapy related toxicity, and 4 died of disease progression. Among the eight primary refractory patients, only one patient who had CNS local disease was alive after chemotherapy with radiation without HDC/SCT. HDC/SCT was done for five patients. Two patients were alive: one survived for 50 months after auto BMT for local mediastinal disease; the other was PR for 5 months after UCBSCT. Among 40 relapsed patients, 2 were alive under chemotherapy alone and gained CR after second line chemotherapy, 1 was alive for 55 months after BM relapse, and 1 was alive for 57 months with radiation after CNS local disease. Among 28 patients who had HDC/SCT after relapse, 12 patients were alive: 7 had had advanced disease and 5 had had local disease.

TABLE I. Patient Characteristics Initial Diagnosis (n = 48)

Age at diagnosis (years), median (range)	9 (1–15)
Male sex (%)	32 (66.7%)
Stage (Murphy's classification)	
I	2
II	7
III	26
IV	13
Histological Immunophenotype	
Precursor B	9
Precursor T	32
Others (not determined 4, NK 2, T, B mix 1)	7

TABLE II. Site of Relapse

Primary site only	6
BM	9
CNS	4
BM and CNS	1
Mediastinum	1
Others	2
Primary site + α*	17

BM denotes bone marrow; CNS, central nervous system; * + α BM, 9; Mediastinum, 4; CNS, 1; Others, 3.

With a median follow-up period of 27.5 months, the 3-year OS rate was 43.2 ± 7.4% (estimate ± SE) (Fig. 3). Univariate analysis identified two features that were significant (Table III) as variables that were predictive of OS: relapse within 12 months and T cell phenotype. The presence of HDC/SCT was not significant. Regarding the total duration of first line therapy, we found no significant difference between 18 months and 24 months ($P = 0.90$). The 3-year progression free survival rate was 37.0 ± 7.3%. Univariate analysis for PFS with the same variables for OS showed a significant difference only in the presence of HDC/SCT (3-year PFS 36.9 ± 9.1% vs. 21.4 ± 11.0, $P = 0.03$).

The OS rates for 25 patients who underwent HDC/SCT during CR or PR, and for 8 patients who received chemotherapy without HDC/SCT after achieving CR or PR were 61.5 ± 10.3% and 37.5 ± 17.1%, respectively; they were not significantly different ($P = 0.06$). Regarding patients who underwent HDC/SCT during CR or PR, 6 among19 patients who underwent allogeneic SCT had relapsed; 4 among 6 patients who had undergone autologous SCT had relapsed. Of those 19 allogeneic SCT recipients, 10 survived without further progression (median 22 months after transplantation), although only 2 of 6 autologous recipients survived (median 40 months). Regarding transplantation-related toxicity, three allogeneic recipients died of toxicity, although none had died with autologous transplantation. Among all transplanted patients, the median times to transplantation from the refractory/relapse phase were 5 months for allogeneic (n = 26) and 4 for autologous (n = 7). BM involvement appeared respectively in 10 cases and 1. The OS rates between these were, respectively 54.0 ± 10.4% and 28.6 ± 17.1%. No significant difference was observed ($P = 0.42$), although a higher OS rate was observed in the allogeneic group. The donor type, whether related or unrelated, also showed no significant difference ($P = 0.86$) among allogeneic transplantation cases. Regarding the transplant preparative regimen, except for one patient who could not undergo the myeloablative regimen, all preparative regimens were myeloablative. Additive chemotherapy varied among patients, for example (ara-C, ara-C + VP-16, VP16 + CY, ara-C + VP-16 + CY, CY + TT, BUS + L-PAM, L-PAM + FDA); no significant difference was found between TBI (n = 22) and non-TBI regimens (9) ($P = 0.73$).

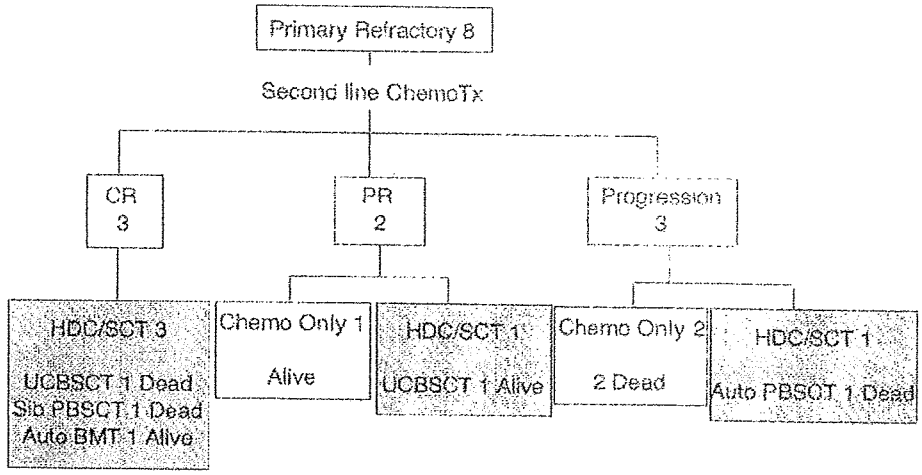

Fig. 1. Clinical courses and final outcomes of primary refractory patients. Tx denotes therapy; CR, complete remission; PR, partial remission; HDC/SCT, high dose chemotherapy and stem cell transplantation; BMT, bone marrow transplantation; Sib, sibling; PBSCT, peripheral blood stem cell transplantation; UCBSCT, unrelated cord blood transplantation.

Based on results of the univariate study (Table III), multivariate analysis was done with an adjustment for relapse within 12 months (vs. beyond), absence of HDC/SCT (vs. presence), Stage III/IV (vs. I/II), cell phenotype (T cell vs. B), and age at diagnosis (10 years and older vs. younger than 10). Histological immunophenotype lost its significance ($P = 0.25$) as a prognostic factor, while relapse within 12 months and absence of HDC/SCT were found to be statistically significant (Table III).

DISCUSSION

Although the prognosis of patients with LBL has been greatly improved, relapsed or primary refractory disease remains difficult to cure. According to the Children's Cancer Group's 5912 study, the survival rate was 33% at 2 years after relapse for 68 patients with non-Hodgkin lymphoma, including 26 LBL [3]. Nationwide studies performed in Austria (one patient survived among four relapsed/progressed LBL) and Germany (4 patients survived among 29 progressive T-LBL) also show poor prognosis of refractory/relapsed LBL [4,8]. In our present study, 3-year OS 43.2% was not satisfactory. Therapy for these patients remains poorly defined. Results of some studies suggest some roles of HDC/SCT for these patients [4,8,9]. Results of the present study show a significant hazard ratio for OS in absence of HDC/SCT. Although some selection bias might affect this retrospective study, it is interesting that it identified the possibility of a benefit of HDC/SCT for relapsed LBL. For acute lymphoblastic leukemia, which shares some characteristics with LBL, HDC/SCT reportedly results in longer

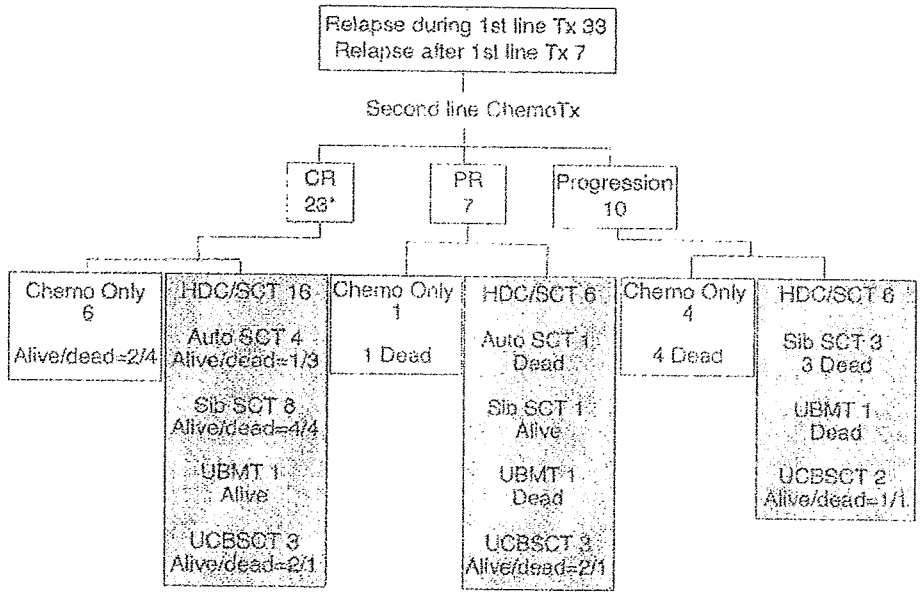

Fig. 2. Clinical courses and final outcomes of recurrent patients. *This includes a patient with unknown subsequent therapy.

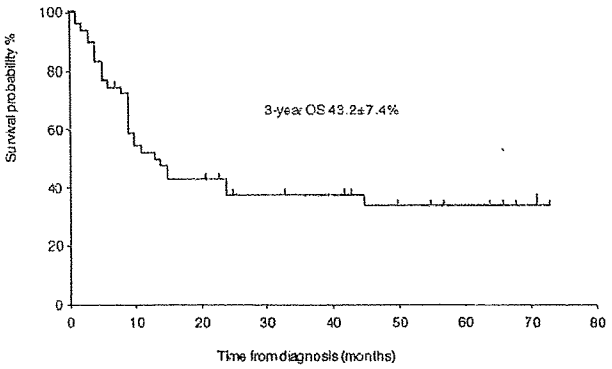

Fig. 3. Kaplan–Meier estimate of overall survival. The median follow-up period was 27.5 months.

leukemia-free survival when compared to outcomes of chemotherapy, especially for patients with poor prognoses [10,11]. However, a CCG1941 prospective study comparing chemotherapy versus HDC/SCT showed no significant advantage for HDC/SCT against chemotherapy for patients relapsing less than 12 months after completion of primary therapy [12]. The UK R1 study also showed that the related allograft was not significantly better than chemotherapy, although there was a moderate EFS benefit, especially in patients with a short first remission [13]. In our study, among 20 patients who relapsed within 12 months from initial diagnosis, 15 received HDC/SCT and 6 got CCR. The remaining 5 patients, all of whom had received chemotherapy, did not survive. Nevertheless, no significance for OS was found between these groups of patients ($P = 0.052$).

For relapsed LBL patients, it is unknown which of allogeneic or autologous is the better donor source. Two recent reports described that allogeneic transplants engendered fewer recurrences but had higher related mortality in LBL patients [14,15]. Burkhardt reported that HDC followed by allogeneic SCT might have beneficial effects in refractory/relapsed cases of T-lymphoblastic lymphoma [8]. Although our study showed no significant difference of survival rates between allogeneic and autologous groups among all transplanted-patients, allogeneic SCT resulted in fewer relapses and progressive diseases than autologous SCT (8 patients among 26 showed relapse or progression after allogeneic transplantation, while 4 among 7 showed relapse or progression after autologous transplantation). Recent progress in supportive therapy during the SCT phase and adaptation to reduced intensity stem cell transplants might reduce transplantation-related mortality and lead to better outcomes [16].

Among the eight patients with primary refractory disease, only three achieved CR under ICE regimen or AML type therapy. For these patients, HDC/SCT was not a suitable salvage therapy. Six patients received allogeneic HDC/SCT as salvage therapy. Among them, only one patient who was on second relapse at the time of this analysis remained alive; all other patients died of recurrence or regimen-related toxicity. Three patients who showed progression after both first and second line chemotherapy died within 6 months from the initial diagnosis. Among 10 patients who showed progression of the disease in spite of second line therapy after relapse, only one patient was alive after UCBSCT. These

TABLE III. Analysis of Variable Factors Against Overall Survival

Factor	3-year OS	*P* for OS*	Hazard ratio	Confidence interval	*P* for OS**
Time of relapse, months					
≤12 (20)	31.9 ± 10.7	0.03	3.60	1.41–9.22	0.007
>12 (20)	51.6 ± 11.7				
Immunophenotype					
T cell (32)	32.8 ± 8.6	0.03	2.45	0.52–11.47	0.25
B cell (9)	72.9 ± 16.5				
Stage					
III/IV (39)	32.1 ± 7.9	0.07	1.55	0.41–5.86	0.51
I/II (9)	88.9 ± 10.5				
Age at diagnosis, years					
≥10 (22)	34.0 ± 10.5	0.09	2.08	0.88–4.92	0.10
<10 (26)	50.9 ± 10.2				
HDC/SCT					
Absence (14)	28.6 ± 12.1	0.10	2.64	1.07–6.52	0.035
Presence (33)	47.2 ± 9.3				
BM+					
Absence (29)	49.5 ± 9.6	0.42	NA	NA	NA
Presence (19)	34.0 ± 11.2				
CNS+					
Absence (40)	44.8 ± 8.2	0.40	NA	NA	NA
Presence (8)	37.5 ± 17.1				
Sex					
Male (32)	39.2 ± 9.3	0.58	NA	NA	NA
Female (16)	50.0 ± 12.5				

BM+, BM involvement at refractory/relapsed phase; CNS+, CNS involvement at refractory/relapsed phase; NA, not applicable; Number of patients are enclosed in parentheses. *P value is calculated using a double-sided log rank test; **Hazard ratio and P value is calculated using a Cox proportional-hazard model.

expressly refractory patients require novel therapeutic agents and strategies.

Predictive factors of poor survival are important when selecting patients for a new experimental therapy. Our data show that the time to relapse has prognostic importance. A BFM group study of relapsed T-cell LBL (29 patients) showed that age, gender, and localization of relapse had no prognostic value, which were same findings of our study. In contrast, they reported that the time of relapse was not associated with the outcome [8].

The outcomes of patients with relapsed/ primary refractory LBL were not satisfactory. However, those who responded to second line chemotherapy showed a respectable chance of survival. For these patients, HDC/SCT was associated with good prognosis. The relative rarity of refractory LBL patients highlights the need for carefully designed clinical trials through multicenter/international collaboration to answer issues of efficient second line chemotherapy, prognostic factors for these refractory patients, and SCT efficacy.

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ORIGINAL REPORT

Impact of the Methotrexate Administration Dose on the Need for Intrathecal Treatment in Children and Adolescents With Anaplastic Large-Cell Lymphoma: Results of a Randomized Trial of the EICNHL Group

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ABSTRACT

Purpose
To compare the efficacy and safety of two methotrexate doses and administration schedules in children with anaplastic large-cell lymphoma (ALCL).

Patients and Methods
This randomized trial for children with ALCL was based on the Non-Hodgkin's Lymphoma–Berlin-Frankfurt-Muenster 90 (NHL-BFM90) study protocol and compared six courses of methotrexate 1 g/m^2 over 24 hours and an intrathecal injection (IT) followed by folinic acid rescue at 42 hours (MTX1 arm) with six courses of methotrexate 3 g/m^2 over 3 hours followed by folinic acid rescue at 24 hours without IT (MTX3 arm). This trial involved most European pediatric/lymphoma study groups and a Japanese group.

Results
Overall, 352 patients (96% ALK positive) were recruited between 1999 and 2005: 175 were randomly assigned to the MTX1 arm, and 177 were assigned to the MTX3 arm. Ninety-two percent of patients received protocol treatment. Median follow-up time is 3.7 years. Event-free survival (EFS) curves were superimposed with 2-year EFS rates (73.6% and 74.5% in the MTX1 and MTX3 arms, respectively; hazard ratio = 0.98; 91.76% CI, 0.69 to 1.38). Two-year overall survival rates were 90.1% and 94.9% in MTX1 and MTX3, respectively. Only two CNS relapses occurred (both in the MTX1 arm). Toxicity was assessed after 2,050 courses and included grade 4 hematologic toxicity after 79% and 64% of MTX1 and MTX3 courses, respectively ($P < .0001$); infection after 50% and 32% of courses, respectively ($P < .0001$); and grade 3 to 4 stomatitis after 21% and 6% of courses, respectively ($P < .0001$).

Conclusion
The results of the NHL-BFM90 study were reproduced in this large international trial. The methotrexate schedule of the NHL-BFM90 protocol including IT therapy can be safely replaced by a less toxic schedule of methotrexate 3 g/m^2 in a 3-hour infusion without IT therapy.

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Anaplastic large-cell lymphoma (ALCL) is a rare disease in children.[1] Most European pediatric groups recommend a treatment with short-pulse chemotherapy based on high-dose methotrexate, cyclophosphamide, vincristine, doxorubicin, and corticosteroids,[2-5] whereas in North America, ALCL patients receive prolonged repeated pulse chemotherapy without high-dose methotrexate.[6] The 2-year relapse rate is approximately 30% with most of these regimens.[2-10] Although the CNS relapse rate is low in previous series of pediatric ALCL, most groups still recommend CNS prophylaxis based on high-dose methotrexate and/or an intrathecal (IT) injection of chemotherapy.[2-6,10] However, the impact of the dose and mode of administration of methotrexate on the risk of systemic and CNS relapses in ALCL patients is unclear.

The Non-Hodgkin's Lymphoma–Berlin-Frankfurt-Muenster 90 (NHL-BFM90) protocol[4] is one of the most attractive treatments in ALCL as a result of the good results obtained in terms of event-free survival (EFS; 5-year EFS, 76%; 95% CI, 67% to 85%) and the lower cumulative doses of drugs, such as alkylating agents, etoposide, and anthracyclines, known to be associated with a risk of long-term toxicity compared with other pediatric and adult protocols. In this protocol, methotrexate was administered at a dose of 0.5 g/m^2 in a 24-hour infusion with IT,[3,4] whereas in studies by other pediatric groups such as in France or the United Kingdom,

methotrexate was administered at a dose of 3 g/m^2 in a 3-hour infusion, with no IT in the French protocol.

Because IT injections impair the quality of life of patients during treatment[11] and may be associated with rare but major complications such as myelopathy, arachnoiditis, or leukoencephalopathy,[12,13] it was decided to ascertain whether the results of the NHL-BFM90 protocol would be maintained by substituting the standard treatment with IT for a higher dose of methotrexate in a shorter infusion without IT. This was the aim of this trial, which compares the efficacy and safety of two methotrexate doses and administration schedules in children with ALCL.

Study Design

This study was an international randomized trial comparing six courses of methotrexate 1 g/m^2 over 24 hours and IT chemotherapy (MTX1 arm) with six courses of methotrexate 3 g/m^2 over 3 hours without IT (MTX3 arm). The main objective of this trial was to estimate the differences in EFS between the MTX3 and the MTX1 arms. Additionally, high-risk patients (defined as patients with mediastinal and/or skin and/or visceral involvement) could enter a second random assignment before the second course that tested the impact on EFS of adding vinblastine during the five latter courses and then weekly for a total duration of treatment of 1 year (vinblastine trial using a factorial design). Only the results of the first random assignment (methotrexate trial) are reported here. Results of the second random assignment (vinblastine trial) will be the subject of a subsequent report.

Eligibility Criteria and Pretreatment Evaluation

This trial was conducted in 12 countries by 10 national or cooperative groups including most European pediatric/lymphoma study groups and a Japanese group. Eligible candidates were patients with biopsy-proven ALCL who were less than 22 years of age. Slides had to be available for a national pathology review. Patients with isolated skin disease, completely resected stage I disease, or CNS involvement were not eligible for the trial. Additional exclusion criteria were previous treatment, congenital immunodeficiency, AIDS, previous organ transplantation, or previous malignancy. Written informed consent had to be obtained. The local ethics committees approved the protocol according to current legislation in each country.

The diagnosis of ALCL was based on morphologic and immunophenotypic criteria and, if possible, on molecular criteria. Mandatory antibodies were CD30, CD15, EMA, ALK1, CD79a, CD20, CD3, CD43, and CD45RO. Slides were reviewed nationally and by an international panel of pathologists blinded to treatment allocation.

Pretreatment Evaluation

Patients underwent a physical examination, a full blood count and biochemical profile, chest/abdominal computed tomography and skeletal scintigraphy, bone marrow aspirate smears and bone marrow biopsies, cerebrospinal fluid cytospin examination, and biopsy of all skin lesions. Patients were staged according to the St Jude and Ann Arbor staging systems. Patients were classified as high risk if they had at least one risk factor, defined as the presence of skin and/or mediastinal and/or visceral involvement (defined as lung, liver, or spleen involvement), and as standard risk if they had no risk factors.

Treatment

Chemotherapy was based on the NHL-BFM90 protocol.[4] All patients received a 5-day prephase followed by six alternating courses (A and B) administered every 21 days (Table 1). The methotrexate dose and administration schedule in courses A and B were randomly allocated before the first course (course A). The duration of chemotherapy between the prephase and the sixth course was 4 months.

Table 1. Chemotherapy Doses and Schedule in Each Course

Course and Drug	Dose and Schedule
Prephase	
Dexamethasone	5 mg/m^2 on days 1 and 2; 10 mg/m^2 on days 3 to 5
Cyclophosphamide	200 mg/m^2 on days 1 and 2
Triple intrathecal injection	Day 1
Course A	
Dexamethasone	10 mg/m^2 on days 1 to 5
Methotrexate	Random assignment* on day 1
Ifosfamide	800 mg/m^2 on days 1 to 5
Cytarabine	150 mg/m^2 × 2 on days 4 and 5
Etoposide	100 mg/m^2 on days 4 and 5
Course B	
Dexamethasone	10 mg/m^2 on days 1 to 5
Methotrexate	Random assignment* on day 1
Cyclophosphamide	200 mg/m^2 on days 1 to 5
Doxorubicin	25 mg/m^2 on days 4 and 5

*Arm MTX1 included methotrexate 1 g/m^2 in 24-hour infusion with triple intrathecal injection at day 1 and leucovorin rescue (15 mg/m^2) at 42, 48, and 54 hours. Arm MTX3 included methotrexate 3 g/m^2 in 3-hour infusion with no intrathecal injection and leucovorin rescue (15 mg/m^2 every 6 hours) starting at 24 hours and ending when the methotrexate level was < 0.15 μm/L. Additionally, high-risk patients could enter the second randomized trial before the first course B (vinblastine trial), which randomly assigned patients to receive or not receive a vinblastine injection (6 mg/m^2) during the five latter courses and then weekly for a total duration of treatment of 1 year.

Response Criteria

Tumor response was evaluated after each course. A comprehensive evaluation had to be performed once all signs of disease had disappeared or no later than after the sixth course. A complete remission was defined as the disappearance of the disease for at least 4 weeks. A residual lesion at the end of treatment was not considered a treatment failure if the residual tumor volume was less than 30% of the initial tumor mass. Follow-up was performed every 2 to 4 months for the first 3 years, every 6 months during years 4 and 5, and then yearly. Relapses were to be confirmed by a biopsy.

Random Assignment

Overall, 175 centers participated in the trial. Random assignment was balanced and stratified according to country and risk group (standard- v high-risk group). Five different data centers managed the random assignment. A centralized randomization software was used in all five data centers except in Italy, with a minimization program (France) or stratified random assignment with permuted blocks of size four (Japan, Germany, and Sweden). In the Italian data center, predefined stratified balanced random assignment lists were used to allocate treatments.

Additionally, high-risk patients could enter a second random assignment before the first course B to receive or not receive vinblastine. This second random assignment was stratified according to country and to treatment allocated by the first random assignment (factorial design).

Statistical Considerations

The primary end point was EFS, which was defined as the time from random assignment to first failure (progression, relapse, second malignancy, or death) or to the last follow-up visit for patients in first complete remission. Secondary end points were overall survival (OS), complete remission, CNS relapse, and acute toxicity.

OS rates were estimated from the date of random assignment to the date of death, whatever the cause, or the date of the last follow-up visit for patients last seen alive. Survival rates (EFS and OS) were estimated using the Kaplan-Meier method with Rothman's 95% CIs.[14] Median follow-up time was estimated using Schemper's method.[15]

Acute toxicity was assessed using the National Cancer Institute Common Toxicity Criteria, version 2.0.[16] Grade 4 hematologic toxicity and grade 3 or 4 nonhematologic toxicity were classified as severe toxicity.

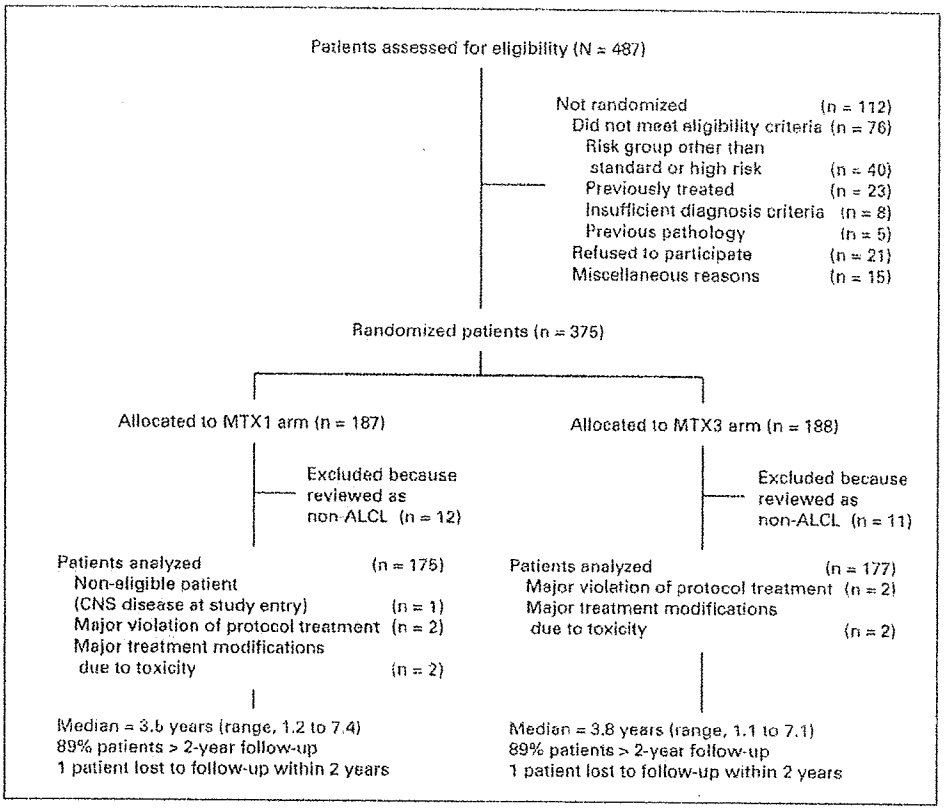

Fig 1. Participant flow CONSORT diagram ALCL, anaplastic large-cell lymphoma

The issue raised in this trial was formulated as a noninferiority question in terms of EFS. Considering the factorial design of the trial, the sample size was determined for the vinblastine trial to demonstrate a reduction of the risk of events by adding vinblastine in high-risk patients. A total of 204 high-risk patients were required for the vinblastine trial. Assuming that the high-risk patients eligible for the vinblastine random assignment accounted for 64% of those eligible for the methotrexate random assignment, we expected to accrue 320 patients (204/0.64) onto the methotrexate trial during accrual onto the vinblastine trial. Given the expected sample size, it was recognized that a noninferiority conclusion could never be proven. Therefore, we planned to only provide CIs for differences in EFS in the two arms.

Planned Analysis

Three planned interim analyses were performed using Fleming's plan[17] and discussed with the independent data monitoring committee (IDMC). The present analysis, which is the final analysis, was performed with a one-sided $P = .0412$. The cutoff date of the present analysis was July 1, 2007.

The main analysis of EFS was to be performed on a modified intent-to-treat population, excluding only the patients for whom the diagnosis of ALCL had been rejected after review. Two secondary analyses were performed, one with no exclusions and the second on a per-protocol population that excluded patients who were not eligible for random assignment, patients for whom the diagnosis of ALCL had been rejected, and patients with a major modification of the allocated treatment.

The hazard ratios (HRs) for events (EFS) and death (OS) and their CIs were estimated using Cox models adjusted by the risk group (standard- v high-risk group) and country and stratified by the treatment allocated by the second random assignment (not randomly assigned, no vinblastine, or vinblastine).

Prespecified secondary analyses, using Cox models, were performed to study variations in the treatment effect according to the risk group, treatment allocated by the second random assignment, and country. Heterogeneity in treatment effects according to country was assessed considering patients from Poland, Belgium, the Netherlands, and Sweden in a unique stratum because of a limited sample size in each of these countries. All reported P values for heterogeneity are two sided.

Toxicity rates between the MTX1 and MTX3 arms were compared using mixed models controlling for the number of the course (course 1 to 6) and the adjunction or not of vinblastine and considering the patient effect as a random effect (repetitive courses per patient). Data were entered and checked with the PIGAS software[18] and analyzed with SAS software (version 8.2; SAS Institute, Cary, NC).

Recruitment and Follow-Up

Between November 1999 and December 2005, 487 patients were screened for study entry. A total of 112 patients were not included in the trial (Fig 1). Thus, 375 patients (91% of the 411 potentially eligible patients) were included.

A central review of the slides was performed for 358 (95%) of 375 patients. The diagnosis of ALCL was rejected in 23 patients. Consequently, 352 patients were included in the main analysis; 175 were assigned to the MTX1 arm, and 177 were assigned to the MTX3 arm.

Baseline Data

The median age at diagnosis was 11.0 years (range, 4 months to 19.5 years). Baseline patient characteristics, overall and by treatment group, are listed in Table 2.

Table 2. Patient Characteristics by Treatment Arm

Characteristic	No. of Patients in MTX1 Arm (n = 175)	No. of Patients in MTX3 Arm (n = 177)	All Patients (N = 352)	
			No.	%
Male	103	108	211	60
Age, years				
< 3	10	9	19	5
3-16	151	157	308	88
> 16	14	11	25	7
Risk group				
Standard risk	65	68	133	38
High risk	109	109	218	62
CNS disease	1	0	1	0.3
"B" symptoms (MD, n = 2)	104	93	197	56
Site of disease				
Peripheral lymph node	150	158	308	88
Mediastinal involvement*	85	82	167	47
Lung lesion*	35	40	75	21
Liver involvement†	30	19	49	14
Spleen involvement†	39	25	64	18
Skin lesion‡	33	35	68	19
Soft tissue mass (MD, n = 1)	32	23	55	16
Bone lesion (MD, n = 43)	21/154	37/155	58/309	19
Bone marrow involvement§	28	14	42	12
St Jude stage				
1	14	10	24	7
2	29	37	66	19
3	106	116	222	63
4	26	14	40	11
Ann Arbor stage				
1	18	11	29	8
2	53	57	110	31
3	50	53	103	29
4	54	56	110	31
International Prognostic Index (MD, n = 73)				
0	22	30	52	19
1	39	40	79	28
2	45	45	90	32
3	34	24	58	21
Allocated treatment by the second random assignment				
No vinblastine	49	51	100	28
Vinblastine	49	47	96	27
Not randomly assigned in the R2 trial	77	79	156	44

Abbreviations: MTX, methotrexate; MD, missing data.
*Radiologic diagnosis by x-ray and/or computed tomography.
†Liver and spleen were considered involved if palpable clinically or enlarged on imaging > 5 cm below the costal margin or nodular on imaging.
‡Skin involvement included biopsy-proven anaplastic large-cell lymphoma cutaneous involvement and clinically diagnosed skin lesions undoubtedly related to anaplastic large-cell lymphoma, with the exclusion of lesions limited to the skin overlying an involved node or a soft tissue mass.
§Bone marrow involvement was defined by the analysis of the bone marrow smears and trephine, using morphologic criteria.

All 352 patients were positive for CD30, 337 (96%) were positive for ALK, and 305 (87%) expressed at least one T-cell marker. According to the WHO classification,[19] which was available for 328 patients, the distribution of the subtypes was as follows: common type (n = 210, 64%), lymphohistiocytic (n = 10, 3%), small cell (n = 21, 6%), giant cell (n = 5, 1.5%), mixed (n = 76, 23%), and Hodgkin's-like (n = 6, 1.8%).

Treatment

Overall, 92% of the patients (162 patients in the MTX1 arm and 163 patients in the MTX3 arm) received protocol treatment of six courses with the planned methotrexate dose according to random assignment. A major protocol violation was observed in four patients (two patients in both arms); the treatment was significantly modified as a result of toxicity in four additional patients (two patients in both arms). These eight patients are included in the main analysis but were excluded from the per-protocol analysis. A modification of the methotrexate dose or of the IT injection in less than three courses was also observed in nine and 10 patients in the MTX1 and MTX3 arms, respectively.

Outcome and Follow-Up

Median follow-up time was 3.8 years from random assignment. Only two patients were lost to follow-up. Disease disappeared completely from all initially involved sites in 309 (88%) of 352 patients.

Among the 43 remaining patients, 14 experienced early progression on treatment, one was not assessable because of an early change of treatment, two died of treatment-related toxicity before achieving a complete remission, and 26 presented with a residual abnormality after the sixth course. Overall, 102 events were reported (treatment-related death, n = 4; early progression, n = 14; and relapse, n = 84). Seventy-three of the 84 relapses occurred during the first 2 years after random assignment. Progression and relapses occurred most frequently at the site of the primary tumor (69%) and were associated or not with new tumor site(s). Only two patients had a CNS relapse as the first event. The 2-year EFS rate of the 352 patients was 74.1% (95% CI, 69.2% to 78.4%).

Overall, 32 deaths were reported (21 as a result of disease progression and 11 as a result of toxicity), including seven deaths after progression or relapse. The 2-year OS rate of the 352 patients was 92.5% (95% CI, 89.3% to 94.8%).

Comparison of Outcome Between Treatment Arms

The outcome results by treatment arm are listed in Table 3. There was no significant difference between the two randomized groups for any of the main and secondary efficacy end points.

The complete remission rates were 89% and 87% in the MTX1 and MTX3 arms, respectively (difference = −2%; 91.76% CI, −8% to 4%). As shown in Figure 2B, the EFS curves were superimposed, with 2-year EFS rates of 73.7% and 74.5% in the MTX1 and MTX3 arms, respectively. The 2-year EFS difference was +0.8% (91.76% CI, −7.3% to 9.0%). The HR for events in the MTX3 arm compared with the MTX1 arm was 0.98 (91.76% CI, 0.69 to 1.38). This result was similar when the strict intent-to-treat population (HR = 1.02; 91.76% CI, 0.74 to 1.42) or the per-protocol population (HR = 1.02; 91.76% CI, 0.72 to 1.45) was considered.

There was no significant heterogeneity in treatment effects in terms of EFS according to country ($P = .86$), risk group ($P = .15$), or the treatment allocated by the second random assignment ($P = .41$). The 2-year OS rates were 90.1% and 94.9% in the MTX1 and MTX3 arms, respectively (Fig 2C). The HR for death in the MTX3 arm compared with the MTX1 arm was 0.67 (91.76% CI, 0.36 to 1.25).

Table 3. Outcome by Treatment Arm

Outcome	No. of Patients	
	MTX1 Arm (n = 175)	MTX3 Arm (n = 177)
Response to chemotherapy		
Complete remission*	155	154
Residual abnormality	10	16
Progressive disease	8†	6†
Not assessed	2	1
Event	51	51
Progression or treatment	8†	6†
Relapse	42	42
Toxic death as first event	1	3
CNS relapse	2	0
Deaths	9	13

Abbreviation: MTX, methotrexate.
*Complete remission was defined as the disappearance of disease from all initially involved sites lasting for at least 4 weeks.
†The eight and six patients with progression on treatment are the same as those listed as having progressive disease under the Response to chemotherapy heading.

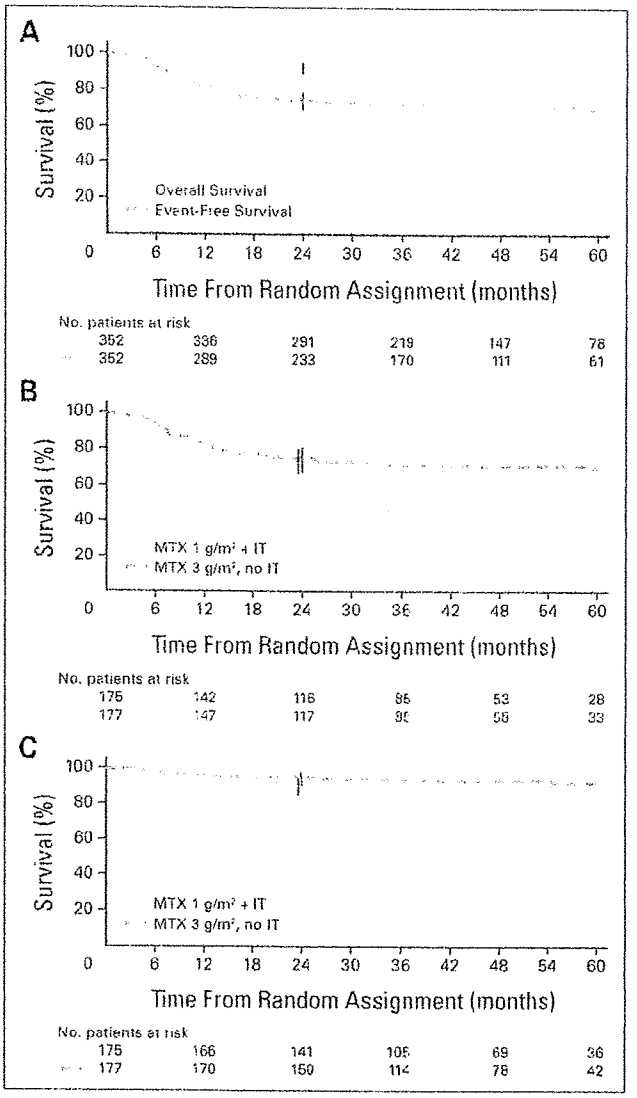

Fig 2. (A) Event-free survival (EFS) and overall survival (OS) of the whole study population. (B) EFS by treatment. (C) OS by treatment. MTX, methotrexate.

Toxicity

Toxicity results are listed in Table 4. Severe toxicity was reported after 75% of courses and consisted mostly of grade 4 hematologic toxicity (72% courses) and grade 3 to 4 mucositis (13%). These toxicities were significantly more frequent after MTX1 courses than after MTX3 courses. The incidence of grade 3 to 4 infection was low (5%) and comparable for both types of courses. However, if all grades of infection are considered, the incidence was significantly higher after MTX1 courses (50%) compared with MTX3 courses (32%; $P < .0001$). No severe complications related to the IT injections were reported.

In this trial, to our knowledge the largest ever conducted in ALCL, we observed that the EFS curve for patients treated with chemotherapy

Table 4. Acute Toxicity According to Treatment Arm

Reported Toxicity	Courses in MTX1 Arm (n = 1,025)			Courses in MTX3 Arm (n = 1,025)*			P†
	No. of Courses With Toxicity	No. of Courses Evaluated	% of Courses With Toxicity	No. of Courses With Toxicity	No. of Courses Evaluated	% of Courses With Toxicity	
All types, all grades	997	1,025	97	941	1,025	92	.002
Severe toxicity	846	1,025	83	701	1,025	68	< .0001
Hematologic grade 4 toxicity	812	1,024	79	655	1,022	64	< .0001
Neutropenia	794	1,024	78	639	1,023	62	< .0001
Anemia	83	1,024	8	50	1,023	5	.06
Thrombocytopenia	215	1,024	21	123	1,021	12	< .0001
Infection							
Grade 3-4	60	1,019	6	50	1,021	5	.32
All grades	508	1,019	50	331	1,021	32	< .0001
Other grade 3-4 toxicity	326	1,025	32	168	1,025	16	< .0001
Stomatitis	210	1,021	21	59	1,023	6	< .0001
Liver toxicity	128	955	13	97	977	10	.06
Miscellaneous	73	1,025	7	56	1,025	5	.13

Abbreviation: MTX, methotrexate.
*Detailed information on all courses (A and B) and toxicity observed after the courses was available for all patients except for one patient on the MTX3 arm.
†P value of the test comparing the toxicity rate between the two treatment groups by the means of mixed models controlling for the number of the course (course 1 to 6), the adjunction or not of vinblastine (treatment allocated by the second random assignment), the type of course (A v B), and the country, considering the patient effect as a random effect (repetitive courses per patient).

based on the NHL-BFM90 protocol with methotrexate at 3 g/m^2 in a 3-hour infusion without IT was superimposable on the EFS curve for patients treated with the same regimen but with methotrexate at 1 g/m^2 in a 24-hour infusion with IT. However, toxicity was significantly reduced in the MTX3 arm.

Conducting such a trial in this rare disease was only possible through the collaboration of European cooperative groups and a Japanese group. The external validity of this study is quite robust because, in all participating groups, most patients with childhood ALCL diagnosed between 1999 and 2006 were screened for trial entry with a random assignment rate of 91% among patients eligible for this trial. Furthermore, initial patient characteristics are those of the target population, as expected from previous reports.[20] The slides of the majority of patients were centrally reviewed, and the diagnosis of ALCL was rejected in only a small number of patients (23 of 358 patients).

The results of the NHL-BFM90 study[4] were reproduced in this international study. The 2-year EFS rate of 74% obtained for the whole trial population compares favorably with the results of previous reports on childhood ALCL.[2-6,9,10]

Although the EFS curves were superimposed, equivalence of the two arms in terms of EFS could not be statistically proven because of the limited number of patients. A total of 2,200 patients would have been required to prove noninferiority of MTX3 compared with MTX1, considering a 5% decrease in the 2-year EFS rate as the maximum allowable difference (limit HR = 1.23). Nevertheless, we were able to exclude the possibility that 2-year EFS of patients treated with MTX3 might be decreased by more than 7.3% compared with the EFS of patients treated with MTX1 with 95% confidence.

We demonstrated that the treatment in the MTX3 arm caused less hematologic and gut toxicity than the treatment in the MTX1 arm despite a higher dose of methotrexate. Decreased toxicity related to a shortened infusion of methotrexate has already been observed by the BFM group in the NHL-BFM95 study comparing methotrexate in a 4-hour infusion with methotrexate in a 24-hour infusion in childhood B-cell non-Hodgkin's lymphoma.[21] In the present study, the interval between the end of the MTX infusion and folinic acid rescue was reduced in the short infusion arm. Therefore, the higher toxicity rate observed in the MTX1 arm may be a result of longer exposure to methotrexate as well as the delayed rescue.

In this study, only two patients had a CNS relapse as a first event. The low incidence of CNS relapses in ALCL has been evidenced in a number of previous reports in children[2,3,5,6,9,10,22-24] and adults.[25,26] However, most pediatric groups still recommend minimal CNS prophylaxis based either on high-dose methotrexate or on IT injections. In previous studies, the 3 g/m^2 dose of methotrexate in a 3-hour infusion was shown to provide potentially cytotoxic concentrations of the drug in CSF for several hours after the infusion.[27] The present study confirms that replacing methotrexate 1 g/m^2 in a 24-hour infusion plus an IT injection with methotrexate 3 g/m^2 in a 3-hour infusion is not associated with any excess CNS relapses in ALCL. Furthermore, the omission of triple IT therapy and the reduction in toxicity in the MTX3 arm should contribute to an improvement in the quality of life of the patients during treatment. Although toxicity was reduced in the MTX3 arm, this regimen still induces substantial acute toxicity. However, the low total doses of anthracyclines (150 mg/m^2 of doxorubicin) and alkylating agents (3.4 g/m^2 of cyclophosphamide and 12 g/m^2 of ifosfamide) in this regimen should avoid long-term complications.

Nevertheless, it is difficult to assess the exact role of high-dose methotrexate in the treatment of childhood ALCL. The results obtained in pediatric ALCL by the Pediatric Oncology Group,[6] with protocols based on doxorubicin, prednisone, and vincristine chemotherapy plus triple IT injections but without high-dose methotrexate, or in adults by several cooperative groups with the cyclophosphamide, doxorubicin, vincristine, and prednisone regimen are similar to those of our study.[28] These protocols are associated with less acute toxicity than the ones described in this study. However, the cumulative doses of anthracyclines and/or alkylating agents are significantly higher than those in the ALCL99 protocol and, therefore, may lead to long-term