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Ⅴ．代表的論文

日本小児臨床薬理学会雑誌　第17巻　第1号　2004年

多施設共同研究の基盤整備について

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Establishment of research basis for multi-center clinical trial of hematological malignancy in children

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要旨

小児造血器腫瘍は、化学療法が最も奏功する悪性腫瘍であり、70％以上に長期生存が可能である。しかし、未だ30％が難治例である一方、治癒率の向上に伴い、成長障害、性腺機能障害、二次がんなどの晩期合併症が問題となっており、より安全で有効な治療法の確立が求められている。また、小児白血病は小児がんの中で最も高頻度であるが、日本での年間発生数は1000人に満たない稀少疾患であり、難治例等の治療法の確立には多施設共同臨床試験が不可欠である。平成14年度に厚生労働科学研究費補助金効果的医療技術の確立推進研究事業（がん分野）に「小児造血器腫瘍の標準的治療法の確立に関する研究」(主任研究者：堀部敬三）が採択され、より質の高い臨床試験を推進するための基盤整備と大規模臨床試験の実施を目指した研究事業が開始された。本研究班では、参加施設基準の設定をはじめ、研究計画書の記載事項および免疫、分子、病理の各診断の標準化を行うことで診断・治療の均質化を図るとともに、臨床試験データの品質管理と保証を行うためにデータセンターを構築し、臨床試験の基盤整備に取り組んでいる。これらの整備によって日本のすべての小児白血病研究グループが共同して質の高い臨床試験を実施することが可能となってきた。また、これを推進するために日本小児白血病リンパ腫研究グループ（JPLSG）が設立された。こうした臨床研究の基盤整備により日本の小児造血器腫瘍の臨床試験の質の向上のみならず医療の均てん化が期待される。

1．緒言

急性リンパ性白血病に代表される小児造血器腫瘍は、化学療法が最も奏功する悪性腫瘍であり、70％以上に長期生存が可能である[1]。しかし、未だ30％が難治例である一方、治癒率の向上に伴い、成長障害、性腺機能障害、二次がんなどの晩期合併症が問題となっており、より安全で有効な治療法の確立が求められている。また、小児白血病は小児がんの中で最も高頻度であるが、日本での年間発生数は1000人に満たない稀少疾患であり、難治例等の治療法の確立には多施設共同臨床試験が不可欠である。平成14年度に厚生労働科学研究費補助金効果的医療技術の確立推進研究事業（がん分野）に「小児造血器腫瘍の標準的治療法の確立に関する研究」（主任研究者：堀部敬三、以下「堀部班」と略す）が採択され、より質の高い臨床試験を推進するための基盤整備と大規模臨床試験の実施を目指した研究事業が開始された。本稿では、これまでの日本の小児造血器腫瘍分野における多施設共同臨床研究の基盤整備の進捗状況と今後の展望について述べる。

2．日本における小児白血病治療研究体制の歴史

小児白血病の治療法は、今まで主に欧米の研究グループによって標準的治療と試験的治療の比較試験を積み重ねることによって開発されてきた。日本でも、1970年代から主に地域単位に欧米の研究成果に基づいて独自のグループスタディが開始された。1980年代には、小児癌白血病研究グループ(CCLSG)、東京小児がん研究グループ（TCCSG）の他、全国各地域に小規模グループが誕生した。また、その頃には予後因子に基づいたリスク分類に従って標準危険群には毒性を軽減した治療法を、高危険群にはより有効な治療法の確立をめざした研究が行われるようになった。その結果、高危険群の中から難治例が明らかにされ、これらの治療法を確立するために1987年にそれまでのグループの枠を超えたAT(Aggressive therapy) 研究会が発足した。AT研究会では、乳児白血病、急性骨髄性白血病（AML)、B細胞性リンパ腫、ダウン症に伴うAMLなど先駆けとなる治療研究が行なわれた。また、1991年からは初の大型研究班として厚生省がん研究助成金「難治性小児がん特に難治性白血病及び類縁疾患の病態の解明と診断・治療法の開発」研究班（主任研究者　長尾　大）が発足し、全国規模のAML共通プロトコール、乳児ALLプロトコールが作成された。この研究班は、その後、月本班（主任研究者　月本一郎)、水谷班（主任研究者　水谷修紀)、中畑班（主任研究者　中畑龍俊）に引き継がれている。また、これまでの小規模グループではエビデンスの創出が困難なだけでなく、1990年代前半に日本のALLの治療成績が伸び悩んだことを踏まえて1996年に北海道、東海、関西、中四国の研究グループ（後に京大グループ、東北グループも参加）が集まり、質の高い臨床研究をめざして小児白血病研究会（JACLS）が設立された[2]。同時期には、初めてのグループ間共同研究として乳児白血病共同治療研究会も活動を開始した。これらの研究は、公的研究助成金や寄付金などで行われてきたが、その額は限られており、臨

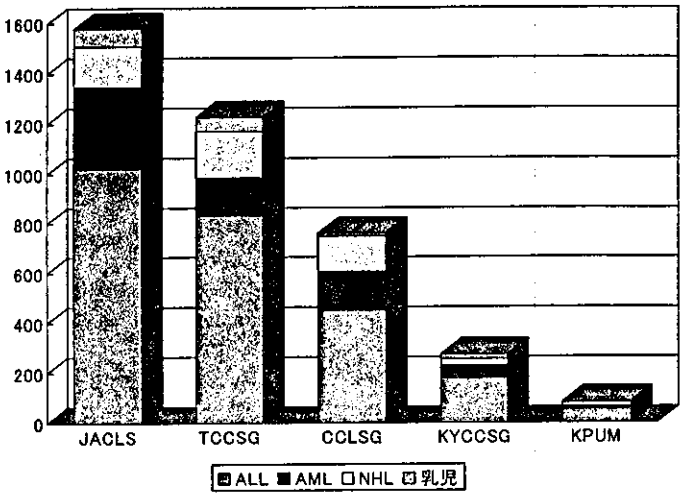

図1 研究グループ別の過去5年間の登録症例数

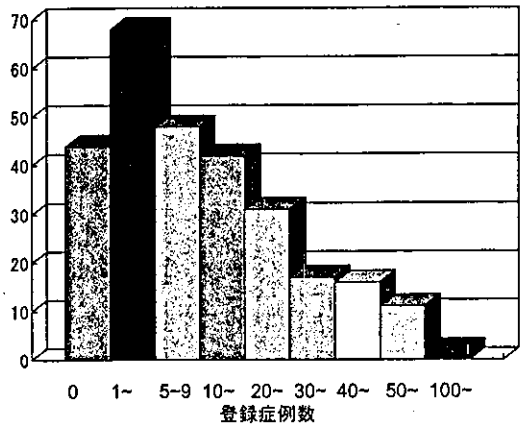

図2 5年登録症例数別の施設数

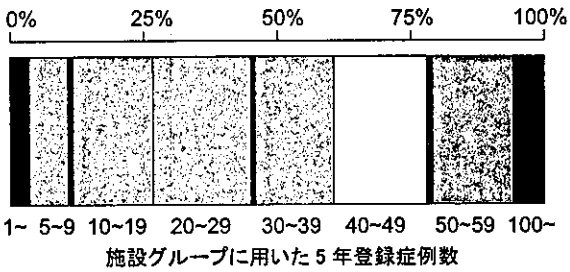

図3 施設を5年登録症例数でグループ化した時のグループ症例数の全症例数に占める割合

床研究体制の整備を十分に行うことは困難であった。さらに問題であったのは、研究者に臨床試験の認識が薄く、プロトコールの倫理審査や納得説明と同意書の作成が必ずしも行われなかったことや治療計画図の配布と実施症例の後付の集計で十分であるとの考え方が一般的であったことである。

これらの問題点を解決して質の高い臨床研究を推進するために平成14年度から厚生労働科学研究として堀部班がスタートした[3]。また、これを受けて2003年には既存の小児がん研究グループのグループ間共同研究組織として日本小児白血病リンパ腫研究グループ（Japanese Pediatric Leukemia/Lymphoma Study Group, JPLSG）が発足した。

3．日本の小児白血病治療研究の現状と問題点

現在、日本には、前述のCCLSG、TCCSG、JACLSの他、九州山口小児がん研究グループ（KYCCSG）、京都府立医科大学グループ（KPUM）を加えた5つの小児白血病研究グループがある。堀部班発足時に各グループの登録データを基に過去5年間の急性白血病、リンパ腫の登録症例数を集計した。その結果、JACLS 1581例、TCCSG 1227例、CCLSG 760例、KYCCSG 273例、KPUM 82例で合計3923例であった（図1）。日本の小児人口を1800万人として造血器腫瘍の発生率を2万人に1人と仮定すると年間900例の新規症例が見込まれる。これに基づくと5つのグループを合わせた症例捕捉率は約90％と考えられた。しかし、病型別の登録症例数の比率はグループ間で格差があり、各グループの登録は、必ずしも全症例が把握されていないと考えられた。臨床試験そのものには全数把握は必要でないが、個々の症例研究の積み重ねが重要な稀少疾患の治療研究においては、研究参加の症例背景に偏りがないかを把握するためにも全症例の前方連続登録が望ましいと考える。

小児白血病の治療研究参加施設は、集計当時は5グループを合わせて279施設に上った。登録症例数に基づいて分類すると5年間で50例以上の登録がある施設は13施設のみであり（図2）、これらの施設の症例数は全体の症例数の21.4％を占めた（図3）。一方、5年間の症例数が1例以上10例未満の施設は合計116施設あり（図2）、これらの施設の症例数は全体の11.5％を占めるに過ぎなかった（図3）。登録ゼロの44施設を除いた5年間登録症例数の中央値は10例であった。集計当時は主要大学は関連病院を含めて集計しているため実際の小児白血病診療施設はさらに多く、その結果、1施設あたりの登録数はさらに少ないと考えられた。全く別組織として診療している関連病院を独立した治療研究施設として扱わないのは研究的にも倫理的にも好ましくなく、臨床試験に際しては研究参加の施設基準を明確にする必要があると考えられる。

また、研究グループ参加施設に対して治療研究実態に関するアンケート調査を実施したところ、臨床試験実施にあたってプロトコールの倫理審査を受けている施設は全体の25.6％

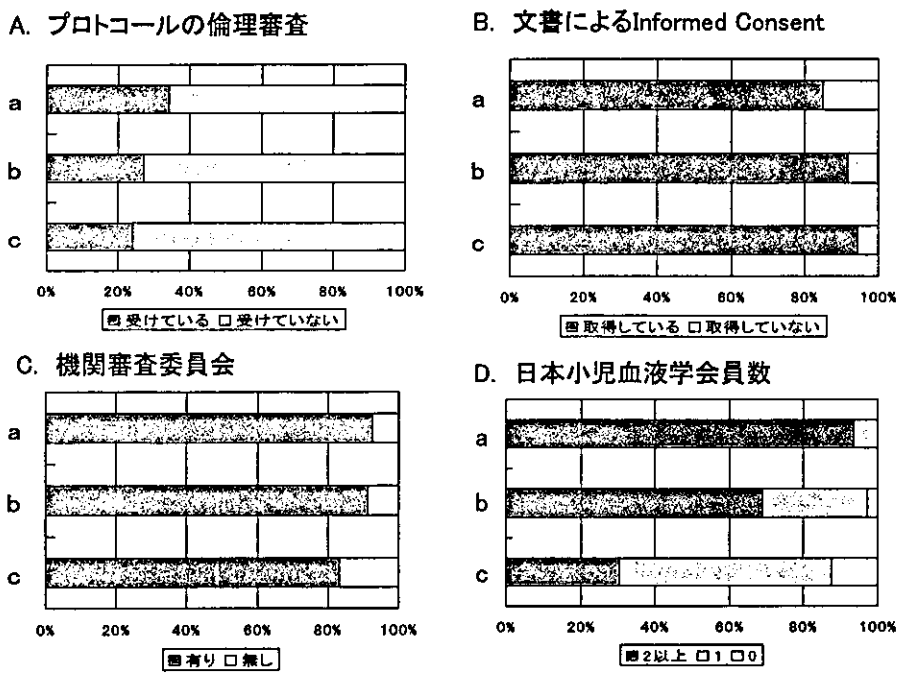

図4　研究グループ参加施設の治療研究実態アンケート結果
(5年登録症例数：a. 30例以上、b. 10例～29例、c. 9例以下)

に過ぎず（図4A)、また、文書による納得説明と同意取得を実施していない施設が未だ8.5％もあった（図4B)。これらは、白血病治療研究が臨床試験として認識されておらずガイドライン治療と混同されていることを反映していると考えられた。さらには、機関審査委員会（IRB）が存在しない施設や日本小児血液学会会員が不在の施設も散見された(図4C, 4D)。一般に、薬剤治験では、新GCP（Good Clinical Practic：医薬品の臨床試験実施の基準に関する省令）基準に準拠して厳しいデータ管理のもとに行われ、登録施設は臨床試験体制が整備され十分な症例登録が期待できる施設に限定される。しかし、治療法確立のための臨床試験は、自主研究グループで行われており、とりわけ，小児がん分野では主治医と患者は常に最新でより良いと思われる治療法を望んでいるためほとんどの患者が臨床試験への参加を希望する。日本では、前述のように1000人に満たない患者を200以上の施設で治療しており、すべての施設に十分な経験のある医師がいるわけではなく、また、経験を積む機会も限られている。このような困難な状況は、主治医の熱意と地域交流で補われてきたと言えるかもしれないが、それだけでは質の高い臨床試験実施は難しく、主治医をはじめとするスタッフ、および参加施設責任者の小児がん治療に対する認識を改める必要があると思われる。

次に、データ管理に関しては、各グループに独自のデータセンターが存在しているものの、実体は、医師および秘書の僅かな手で登録、データ入力、データクリーニングが行われている。つまり、症例の適格性のチェック、フローシートの回収、データのバリデーションなど膨大なデータ管理業務をこなすにはマンパワー不足は否めず、十分な品質管理が行われているとは言い難い。専任の中央データマネジャーおよび施設の臨床試験コーディネーターなくしては質の高いデータ管理は困難である。また、これまでのデータ解析はプロトコール委員会の解析担当者が行う場合が多く、生物統計家は必ずしも関与してこなかった。このように、小児白血病治療研究における臨床試験データ管理は、未だ不十分と言わざるを得ず、効率的で信頼性の高いデータ管理体制の確立が急務であると考えられる。

4．堀部班の役割とこれまでの成果

堀部班の目的は、小児造血器腫瘍の根拠に基づいた医療(Evidence-based Medicine，EBM）を推進するための研究体制整備と大規模臨床試験の実施である。より優れた治療法は、臨床試験によるエビデンスを積み重ねて創り上げられる。すなわち、臨床試験には、エビデンスが期待できるだけの科学性とヒトを対象とした実験であるが故の倫理性が求められている。これは、複雑な治療スケジュールが行われる造血器腫瘍においても例外ではない。これらの目的を達成するために、堀部班では表1に示すプロジェクトを計画実施している。

臨床研究において研究結果の正当性を確保するには、研究デザイン立案から結果（データ）の解析とその解釈に至るすべての過程で起こりうるエラーを排除する必要がある。そのためには、研究デザイン、診断、治療、データ管理、解析の各々に高い品質が求められる。研究デザインの質の確保には、プロトコール立案時から生物統計家の参加が必要である。また、研究計画書には診断から治療終了までの必要事項がもれなく記載される必要があり、さらに、各項目についても解釈が参加施設間で異ならないように内容を周知する必要

表1　堀部班のプロジェクト

1.	臨床データ管理システムの確立
2.	臨床研究における倫理的配慮の確立
3.	免疫学的診断の標準化
4.	分子・細胞遺伝学的診断の標準化
5.	病理学的診断の標準化
6.	乳児白血病の標準的治療法の確立
7.	小児フィラデルフィア染色体陽性ALLの標準的治療法の確立
8.	小児成熟B細胞型リンパ腫の標準的治療法の確立
9.	小児リンパ芽球型リンパ腫の標準的治療法の確立
10.	小児未分化大細胞型リンパ腫の標準的治療法の確立
11.	小児AMLの標準的治療法の確立
12.	ALL治療層別法の標準化

がある。堀部班では、これらのことを標準化するためにプロトコールマニュアルを作成するとともに、名古屋医療センター臨床研究センター内にデータセンターを設立し、専任の医師、データマネジャー、クラーク、システム開発担当を配置してプロトコールごとにプログラムを作成し、登録からデータクリーニング、モニタリングレポートまでを一貫して行えるデータ管理体制を構築した。データ管理については、新規試験での実施は少ないものの、全国の40％の症例を捕捉するとされる小児白血病研究会のALL-02臨床試験のデータ管理の経験を通してさまざまな問題点が明らかにされており、引き続き参加施設の啓蒙とともに臨床試験支援が必要と考えられた。

また、診断の質の向上と標準化のために免疫学的診断、分子・細胞遺伝学的診断、病理学的診断のワーキンググループ（WG）をそれぞれ設けて診断基準等を作成した。免疫学的診断WGでは、小児急性白血病の免疫学的診断に有用なマーカー解析パネルを定めた。分子・細胞遺伝学的診断WGでは、検体の採取、運搬、保存等の標準化と遺伝子検査を診断上の必要度に応じたランク付けを行った。病理学的診断WGでは、リンパ腫の全国病理中央診断に向けて体制整備を行っている。

治療の質を確保するためにプロトコールマニュアルで治療の具体的手順や変更基準および方法を示して臨床試験における治療の均質化を試みた。さらに、倫理性の確保の点から最低限の参加施設基準を設けた。すなわち、日本小児血液学会会員がいること、倫理委員会または機関審査委員会(IRB)があること、プロトコールが遵守できること、5年間で5例以上の登録が見込めること、とした。

さらに、倫理問題検討WGにおいて、検体保存と研究利用にあたっての問題点を抽出し、匿名化、説明と同意の取得、検体保存施設、検体供給、検体保存期間、研究審査委員会等について検討し、これらに関する規約および手続き方法を検討中である。また、臨床試験の科学性と倫理性を担保するために、臨床試験の実施には日本小児血液学会臨床研究審査検討委員会の承認を必要とすることとした。

これらの基盤整備のもとに以下の臨床試験が進んでいる。小児未分化大細胞型リンパ腫（ALCL）は、日本として欧州小児リンパ腫グループの臨床試験ALCL99に参加し、2002年6月より試験を実施中である。乳児ALLは、乳児MLL遺伝子再構成陽性ALLを対象に造血幹細胞移植の早期導入の有用性を検証する臨床試験MLL03を計画し2004年2月に試験を開始した。さらに5つの臨床試験：小児Ph1-ALLに対する造血幹細胞移植を前提とした治療戦略におけるimatinib mesylateの有用性を検証する臨床試験PhALL03、小児成熟B細胞性腫瘍に対する短期集中型臨床試験B-NHL03、その付随研究として顆粒球コロニー刺激因子（G-CSF）の予防的投与の有用性に関するランダム化比較試験、小児リンパ芽球型リンパ腫に対する標準的治療法の確立ためにBFMプロトコールを土台とした臨床試験LLB-NHL03/ALB-NHL03、が計画され、現在プロトコール審査中である。さらに、小児急性骨髄性白血病（AML）については、ダウン症に伴うAML、急性前骨髄球性白血病、狭義のAMLに分けて治療研究が検討されている。

5．日本小児白血病リンパ腫研究グループ（JPLSG）の設立

このような質の高い臨床試験を円滑に進めるには、各研究グループの協調としっかりした財政基盤の確立が必要である。そのために、国内の小児がん研究グループの共同研究を推進する組織と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。各グループから選出された委員により運営委員会、代議員会、各治療研究委員会などの委員会を構成し、広く参加施設の意見を集約できる組織とした。また、財団法人がんの子供を守る会の支援事業に位置づけていただき、広報活動を通じて財政および雇用の安定を図る計画である。現在、規約および各種委員会を整備し、質の高い臨床試験の遂行が可能な組織を構築中である（図5）。現在、予定されている臨床試験への参加状況を図6に示す。これにより、わが国の小児がん治療においてエビデンスに基づいた統一的な標準治療が確立していくものと期待される。

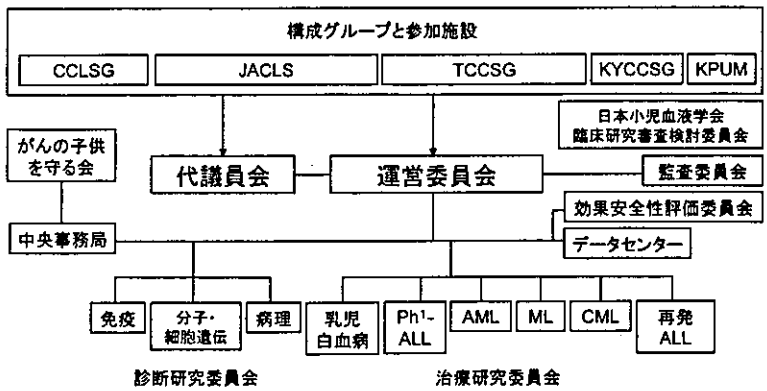

図5 日本小児白血病リンパ腫研究グループ（JPLSG）の組織図

研究グループ	乳児ALL	Ph1-ALL	リンパ腫	AML
CCLSG	○	○	○	△
JACLS	○	○	○	○
TCCSG	○	○	○	○
KYCCSG	○	×	○	○
KPUM	○	×	×	○

図6 JPLSG臨床試験への参加状況

6．おわりに

70％以上の小児白血病患者で長期生存が可能になった現在もなお白血病治療はまだまだ実験的治療である。白血病がヘテロな疾患群であることが明らかとなり、国際共同研究なくしては稀少疾患である小児白血病の標準的治療法の確立は困難となってきている。欧米では、すでにそれを克服するための国際共同研究体制作りが始まっている[4]。日本がそれに取り残されないためにもJPLSGの体制整備と、全国的、世界的視野での臨床研究の推進が求められている。

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Infant acute lymphoblastic leukemia with *MLL* gene rearrangements: outcome following intensive chemotherapy and hematopoietic stem cell transplantation

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Forty-four infants with acute lymphoblastic leukemia (ALL) characterized by *MLL* gene rearrangements were treated on a protocol of intensive chemotherapy followed by hematopoietic stem cell transplantation (HSCT) between November 1998 and June 2002. The remission induction rate was 91.0%, and the 3-year overall survival and event-free survival (EFS) rates, with 95% confidence intervals, were 58.2% (43.5%-72.9%) and 43.6% (28.5%-58.7%), respectively. Univariate analysis of EFS by presenting features indicated a poorer outcome in patients younger than 6 months of age with high white blood cell counts (≥ 100 × 10^9/L; EFS rate, 9.4% versus 55.1% for all others, $P = .0036$) and in those with central nervous system invasion (EFS rate, 10.0% versus 56.9% for all others, $P = .0073$). The 3-year posttransplantation EFS rate for the 29 patients who underwent HSCT in first remission was 64.4% (46.4%-82.4%). In this subgroup, only the timing of HSCT (first remission versus others) was a significant risk factor by multivariate analysis ($P < .0001$). These results suggest that early introduction of HSCT, possibly with a less toxic conditioning regimen, may improve the prognosis for infants with *MLL*$^+$ ALL. Identification of subgroups or patients who respond well to intensified chemotherapy alone should have a high priority in future investigations. (Blood. 2004;104:3527-3534)

Introduction

Despite remarkable advances in the treatment of childhood acute lymphoblastic leukemia (ALL), especially with the introduction of intensive multiagent chemotherapy, infants with this disease continue to have a poor prognosis.[1,2] Their leukemic cells are characterized biologically by a lack of the early lymphocyte antigen CD10 and by 11q23 translocations/*MLL* gene rearrangements, the latter feature being associated with a highly distinct gene expression profile and a poor outcome in most treatment programs.[3,4] Especially dire is the prognosis for infants with the 4;11 translocation, the vast majority of whom have a relapse and die of progressive disease.[5,6] On the other hand, several groups have indicated that a good initial steroid response and 11q23 translocations other than the 4;11 translocation predict a more favorable outcome in infants with ALL.[7,8] Recently, Pui et al[9] reported that age under 1 year and *MLL* rearrangements are the most adverse risk factors in childhood ALL, underscoring the clinical significance of these 2 characteristics. Thus, improving the prognosis of infant ALL will likely require innovative strategies in which patients with or without *MLL* gene rearrangements are regarded as discrete subgroups requiring different treatment protocols.

The role of hematopoietic stem cell transplantation (HSCT) in the management of infants with ALL is still unclear,[10] primarily because only small numbers of patients with documented *MLL*$^+$ ALL have been treated with this modality in reported series.[11-13] Between 1996 and 1998, we implemented a prospective treatment protocol (MLL96) that stratified infant ALL patients according to the presence or absence of *MLL* gene rearrangements; infants with *MLL*$^-$ ALL were treated with standard chemotherapy only, whereas those with *MLL*$^+$ disease were given intensive chemotherapy followed by HSCT.[14] Unfortunately, the results were not satisfactory, as demonstrated by a 3-year event-free survival (EFS) rate of only 34.0% in the *MLL*$^+$ subgroup, reflecting a high relapse rate during the first 6 months of chemotherapy and before HSCT. However, the outcome in patients undergoing HSCT in first remission was superior to that in patients receiving transplants later, suggesting an advantage from early introduction of HSCT.

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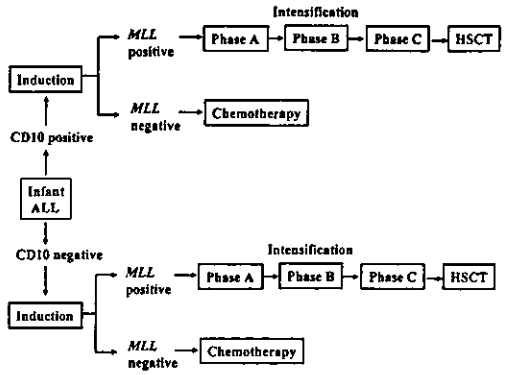

Figure 1. Flow diagram illustrates the design of the MLL98 protocol. Each infant presenting with ALL was assigned to one of 2 subgroups at diagnosis according to the expression of CD10 antigen on leukemic blast cells. Patients were reassigned to subgroups based on the detection of *MLL* gene rearrangements after remission induction. Those with *MLL*$^+$ blasts received 3 courses of intensification therapy followed by HSCT. Chemotherapy regimens for *MLL*$^+$ cases are reported in Table 1.

Consequently, to prevent early relapse in this subgroup, we instigated treatment protocol MLL98, which specified more intensive chemotherapy and HSCT early in first remission (3-5 months after diagnosis). Here we describe the effectiveness and toxicity of this protocol, as well as the prognostic factors that appear to discriminate between subgroups of infants with a better or worse risk of treatment failure.

Patients, materials, and methods

Patients

Between November 1998 and June 2002, 54 infants younger than 12 months of age at the time of diagnosis of ALL were registered with the Japan Infant Leukemia Study Group and treated on the MLL98 protocol. In a nationwide surveillance study, the incidence rate of new infant ALL cases was calculated as 20/y (96 cases between 1997 and 2001; K.H., unpublished data, March 2003). Therefore, the current study included approximately 80% of all infants diagnosed with ALL in Japan over the 3.5-year enrollment period. Written informed consent was obtained from the parents of all patients at the time of enrollment, and all aspects of this investigation were approved by the appropriate institutional review boards. Prior to treatment, each patient was evaluated with respect to the characteristics of the leukemic cells, including immunophenotype, cytogenetics, and *MLL* gene rearrangement. The diagnosis of ALL was based on more than 30% lymphoblasts in the bone marrow (BM), with less than 3% staining positively for myeloperoxidase (MPO). Central nervous system (CNS) invasion was defined as more than 5 mononuclear cells per microliter of cerebrospinal fluid with obvious lymphoblasts.

Immunophenotype, cytogenetics, and detection of *MLL* gene rearrangements

Cell surface markers were analyzed with an EPICS-PROFILE flow cytometer (Coulter Electronics, Hialeah, FL) at our central laboratory. Surface antigens studied in this investigation were as follows: CD10, CD19, and CD20 (B-cell markers); CD2, CD3, cytoplasmic CD3, CD4, CD5, CD7, and CD8 (T-cell markers); and CD13, CD14, CD33, cytoplasmic MPO, CD41, and glycophorin A (myeloid-cell markers). HLA-DR and CD56 served as additional cell markers. A positive reading for each antigen was defined as reactivity by 25% or more of the leukemic cells. Cytogenetic analysis of leukemic cells was performed by a G-banding technique. The presence of *MLL* gene rearrangements was determined by Southern blot analysis, as described previously.[14] Briefly, DNA extracted and digested with *Bam*HI and *Hin*dIII was hybridized with a cDNA probe covering the breakpoint cluster region of the *MLL* gene.

Treatment protocol

All infants enrolled in this study were treated according to the MLL98 protocol (Figure 1; Table 1). Each patient was assigned to a subgroup according to the presence or absence of CD10 expression at diagnosis (CD10 negativity correlates closely with *MLL* gene rearrangement[6]). The subgroup assignments were reassessed when the presence or absence of an *MLL* gene rearrangement was determined by Southern blot analysis.

Table 1 presents the details of the protocol for infants with *MLL*$^+$ ALL. Those with CD10$^+$ ALL received an induction regimen of vincristine (VCR), doxorubicin (DXR), cyclophosphamide (CPA), L-asparaginase (ASP), and dexamethasone (DEX) or prednisolone (PSL) for 4 weeks, followed by etoposide (VP-16) and cytarabine (Ara-C) for 4 days. Those with CD10$^-$ ALL received VCR, DXR, CPA, and DEX for 2 weeks followed by VP-16 and Ara-C for 4 days. Depending on the results of Southern blot analysis, the subgroup with *MLL*$^-$ ALL was then given 2 years of standard chemotherapy that included consolidation, intensification, reinduction, and maintenance phases. With the exception of VCR, drug dosages were based on body surface area rather than body weight, the method used our previous investigation.[14] This change increased the dosage of all antileukemic drugs by 1.2- to 2-fold. Thus, total doses of drugs other than VCR were reduced by one third in patients younger than 2 months and by one fourth in those 2 to 4 months of age. Patients with molecularly confirmed *MLL*$^+$ ALL received 3 courses of intensification chemotherapy, as described in Table 1, and then underwent HSCT. The intent was to perform transplantation in all patients in first remission preferentially within 3 to 5 months after diagnosis; however, those who had relapses before HSCT underwent the procedure at relapse or in second remission. The conditioning regimen consisted of a combination of total body irradiation (TBI; 2 Gy, twice a day on days −7 to −5 for a total of 12 Gy), VP-16 (60 mg/kg on day −4), and CPA (60 mg/kg on days −3 to −2 for a total of 120 mg/kg) or a combination of busulfan (BU; 35 mg/m,^{2} 4 times a day on days −8 to −5 for a total of 560 mg/m^2), VP-16, and CPA.

Table 1. Pretransplant chemotherapy for patients with *MLL*$^+$ ALL*

Regimen	Dosing schedule
Induction therapy	
VCR	0.05 mg/kg, IV, days 1 and 8
DEX	10 mg/m^2/d in 2 divided doses, IV, days 1-14
CPA	1200 mg/m^2, DIV, day 2
DXR	25 mg/m^2, IV or DIV, days 3 and 5
VP-16	100 mg/m^2, DIV, days 15-18
Ara-C	500 mg/m^2, DIV, days 15-18
TIT	Days 1 and 15
Intensification therapy	
Phase A	
VP-16	100 mg/m^2, DIV, days 1-3
Ara-C	200 mg/m^2, DIV, days 4-8
THP-DXR	30 mg/m^2, IV or DIV, days 4 and 5
PSL	60 mg/m^2/d in 3 divided doses, PO, days 4-9
ASP	20 000 U/m^2, DIV, day 9
TIT	Day 1
Phase B	
VCR	0.05 mg/kg, IV, day 1
DEX	10 mg/m^2/d in 2 divided doses, PO, days 1-7
MTX	3000 mg/m^2/24 h, DIV, day 1
Folinic acid	15 mg/m^2 (36 hours after the start of MTX, 7 times)
CPA	600 mg/m^2/d in 2 divided doses, DIV, days 2 and 3
TIT	Day 1
Phase C	
MIT	10 mg/m^2, IV or DIV, day 1
VP-16	100 mg/m^2, DIV, days 1-5
Ara-C	3000 mg/m^2, DIV, days 1-5
TIT	Day 1

VCR, vincristine; DEX, dexamethasone; CPA, cyclophosphamide; DXR, doxorubicin; VP-16, etoposide; Ara-C, cytarabine; TIT, triple intrathecal therapy (age < 3 months: MTX, 3 mg; hydrocortisone, 10 mg; Ara-C, 6 mg; age ≥ 3 months: MTX, 6 mg; hydrocortisone, 10 mg; Ara-C, 12 mg); THP-DXR, tetrahydropyranyl doxorubicin; PSL, prednisolone; ASP, L-asparaginase; MTX, methotrexate; MIT, mitoxanthrone; IV, intravenously; DIV, drip intravenously; PO, by mouth.

*The dose of each drug except VCR was reduced by one third in patients younger than 2 months and by one fourth in those 2 to 4 months of age.

Table 2. Presenting characteristics and initial outcome in 44 infants with *MLL*⁺ ALL

Feature with subcategories	No.
Gender	
Male	19
Female	25
CD10 antigen	
Positive	3
Negative	41
Age at diagnosis, mo	
Median	5
Range	0-11
WBC count, ×10⁹/L	
Median	129
Range	1.7-1524
CNS invasion	10/41
Karyotype	
4;11 translocation	27
11;19 translocation	4
9;11 translocation	3
Other	2
Normal	8
Outcome	
Induction failure	1
Death during induction	2
Relapse	17
BM	12
CNS	4
BM/CNS	1
Death in CCR after HSCT	4
Refusal of treatment after CR	1
CCR	19

CCR indicates continuous complete remission.

Prophylaxis for graft-versus-host disease (GVHD) consisted of either cyclosporin A (CSA) or FK506 (FK) combined with short-term methotrexate (MTX).

Statistical analysis

Comparisons of continuous variables (eg, age, white blood cell [WBC] count, time to transplantation) were made with the Mann-Whitney *U* test. Differences in the distribution of categorical variables (eg, gender, WBC count, age, CNS invasion at diagnosis, karyotypes, and remission status at HSCT) were analyzed with Fisher exact test. Overall survival (OS) and event-free survival (EFS) rates with 95% confidence intervals (CIs) were estimated by the Kaplan-Meier method and compared with use of the log-rank test. Multivariate analysis of survival was performed with the Cox proportional hazard model and a stepwise regression method. OS was calculated for the period from the day of diagnosis until the day of death due to any cause. EFS was calculated from the day of diagnosis until the date of an adverse event: relapse, diagnosis of a secondary cancer, or death due to any cause. Patients failing to respond to induction therapy were assigned an EFS time of zero. In comparisons of EFS between patients undergoing HSCT in first remission or in some other state, the duration of EFS, considered as posttransplantation time, was calculated from the day of transplantation until the earliest date of any adverse event, as defined. All results were updated to April 30, 2004.

Results

Patient characteristics

Altogether, 54 infants were enrolled in the MLL98 study. Among the 44 *MLL*⁺ patients, 3 were CD10⁺ and therefore received induction therapy specified for patients with that marker. Each of the remaining 41 patients, all of whom were CD10⁻, received the more aggressive induction therapy described in Table 1. These 44 patients were given 3 courses of intensification therapy after molecular confirmation of *MLL* positivity. Table 2 presents the clinical characteristics of the 44 *MLL*⁺ ALL infants (19 boys and 25 girls). The median WBC count at diagnosis was 129 × 10⁹/L, and there was a high incidence (24.4%) of CNS involvement. The 4;11 translocation was detected in 27 cases (61.4%) by chromosomal analysis, and 8 patients had normal karyotypes despite the presence of *MLL* gene rearrangements by Southern blot analysis.

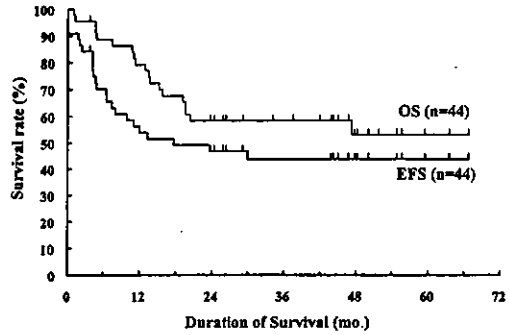

Figure 2. OS and EFS rates for 44 infants with *MLL*⁺ALL. The estimated rates at 3 years were 58.2% (95% CI, 43.5%-72.9%) and 43.6% (28.5%-58.7%), respectively. Tick marks represent patients still at risk of death or other adverse event.

Treatment results

Remission induction and 3-year OS and EFS rates among the infants with *MLL*⁺ALL were 91.0%, 58.2% (95% CI, 43.5%-72.9%), and 43.6% (28.5%-58.7%; Figure 2), respectively; the median duration of observation was 785 days. Among the 41 infants who achieved complete remission (CR), 12 had relapses in the BM, 4 in the CNS, and 1 in the BM/CNS; 19 remained in remission (Table 2). Relapse occurred before HSCT in 11 patients and later in 7 (including 1 patient who failed to respond to induction therapy). Of the 5 patients who were saved, 2 continued in remission after first HSCT and 3 after a second HSCT.

Log-rank comparison of EFS rates by selected clinical and biologic features of the *MLL*⁺ infants (Table 3) generally failed to

Table 3. Comparison of 3-year EFS rates by presenting features in infants with *MLL*⁺ ALL

Feature	No. of patients	EFS (%)	*P*
Age, mo			
Younger than 6	25	28.0	.0499
6 or older	19	63.2	
Gender			
Male	19	44.9	.8470
Female	25	42.7	
WBC count, ×10⁹/L			
Less than 100	20	53.3	.1867
100 or higher	24	35.2	
Less than 200	30	46.9	.5861
200 or higher	14	35.7	
Less than 300	35	46.1	.7018
300 or higher	9	33.3	
CNS involvement			
Positive	10	10.0	.0073
Negative	31	56.9	
Karyotype			
4:11 translocation	27	37.0	.1763
Other	17	56.3	

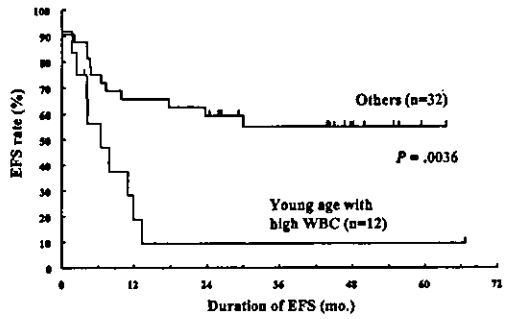

Figure 3. Comparison of EFS rates for infants with *MLL*⁺ ALL stratified by age and WBC count at diagnosis. The outcome for patients younger than 6 months with high WBC count (≥ 100 × 10^9/L) was significantly worse than that associated with the corresponding favorable characteristics ($P = .0036$). Tick marks represent patients still at risk of death or other adverse events.

demonstrate statistically significant relationships. However, patients with CNS invasion at diagnosis and those younger than 6 months had a significantly poorer prognosis than those without these characteristics. An especially poor outcome was noted in infants younger than 6 months who presented with a WBC count of ≥ 100 × 10^9/L: 3-year EFS, 9.4% versus 55.1%, $P = .0036$ (Figure 3).

Of the 38 infants who underwent HSCT, 29 were in first remission and 9 in second remission or relapse (Table 4). Eighteen in first remission underwent transplantation within the specified 3- to 5-month window after diagnosis. Six patients did not undergo HSCT, 3 because of very early relapse and 1 because of parental refusal (these 4 infants died as a result of disease progression), and 2 because of fatal viral infections that developed during induction therapy. Unrelated cord blood transplantation (UCBT), related

Table 4. Characteristics and outcome of HSCT in 38 patients with *MLL*⁺ ALL

Age, mo/gender	WBC count, ×10^9	HSCT				Conditioning regimen	GVHD prophylaxis	Outcome
		Type	Status	HLA*	Time, mo†			
5/F	260	UCBT	CR1	4/6	4	BU	CSA	CCR
6/M	21	UCBT	CR1	5/6	5	TBI	CSA	CCR
7/F	24	UCBT	CR1	5/6	4	BU	FK	CCR
7/F	668	UCBT	CR1	5/6	5	TBI	FK	CCR
6/F	420	UCBT	CR1	5/6	6	TBI	CSA	CCR
4/F	7	UCBT	CR1	5/6	4	TBI	CSA	Rel‡
11/M	119	UCBT	CR1	6/6	5	TBI	FK	CCR
4/F	5	UCBT	CR1	5/6	6	TBI	CSA	Rel§
6/M	39	UCBT	CR1	5/6	5	BU	CSA	CCR
4/M	1000	UCBT	CR1	4/6	5	BU	CSA	Fail"
5/M	26	UCBT	CR1	6/6	6	BU	CSA	CCR
1/M	39	UBMT	CR1	6/6	5	TBI	FK	CCR
3/F	143	RPBSCT	CR1	5/6	7	BU	CSA	Rel§
7/F	2	UCBT	CR1	4/6	8	TBI	FK	CCR
2/F	48	RBMT	CR1	6/6	5	BU	CSA	CCR
4/M	552	UCBT	CR1	5/6	6	TBI	FK	Rel‡
4/F	35	RBMT	CR1	4/6	4	TBI	FK	CCR
6/M	1524	UBMT	CR1	6/6	6	BU	FK	CCR
11/F	299	UCBT	CR1	5/6	5	BU	CSA	CCR
9/F	251	UCBT	CR1	4/6	3	TBI	FK	D¶
9/F	732	RBMT	CR1	6/6	4	TBI	CSA	Rel‡
3/M	54	UCBT	CR1	5/6	5	TBI	FK	Rel#
7/M	1252	UCBT	CR1	6/6	6	BU	CSA	Rel#
1/M	44	UCBT	CR1	5/6	6	TBI	FK	D¶
10/M	31	UBMT	CR1	6/6	8	Other	FK	CCR
4/F	23	UCBT	CR1	5/6	5	BU	FK	CCR
11/F	143	RBMT	CR1	5/6	5	TBI	CSA	CCR
4/F	50	RPBSCT	CR1	5/6	5	BU	FK	CCR
7/M	124	UCBT	CR1	4/6	6	BU	CSA	CCR
6/M	47	UCBT	CR2	6/6	4	TBI	CSA	Rel#
3/F	288	UCBT	CR2	5/6	5	TBI	CSA	CCR
0/M	24	UCBT	CR2	5/6	3	BU	FK	D¶
3/F	134	UCBT	IF	4/6	4	TBI	CSA	Rel‡
4/F	225	RBMT	Rel	6/6	8	BU	CSA	CCR
7/F	11	UCBT	Rel	5/6	6	TBI	CSA	Rel§
2/M	54	RBMT	Rel	5/6	11	Other	FK	Rel‡
2/F	188	UBMT	Rel	6/6	5	BU	FK	Rel‡
1/M	900	UCBT	Rel	6/6	5	TBI	FK	Rel‡

CR1 indicates first remission; FK, FK506; Rel, relapse; Fail, failure of transplantation; D, death; CR2, second remission; IF, induction failure. Other abbreviations are explained in the text and Tables 1 and 2.

*HLA results: 6/6, complete match; 5/6, 1-locus mismatch; 4/6, 2-loci mismatch.

†Time from diagnosis to HSCT.

‡Death due to disease progression without second HSCT.

§Death due to disease progression after second HSCT.

"Toxic death after second HSCT.

¶Toxic death without second HSCT.

#CCR after second HSCT.

bone marrow transplantation (RBMT), unrelated bone marrow transplantation (UBMT), and related peripheral blood stem cell transplantation (RPBSCT) were performed in 26, 6, 4, and 2 patients, respectively (Table 4). The median time to transplantation, regardless of the source of stem cells, was 5 months. The type of HSCT was decided on by each participating investigator, based on the availability of suitable donors at the time of transplantation. The HLA disparities at low resolution in the patients who received UCBT were complete match in 5, 1-locus mismatch in 15, and 2-loci mismatch in 6. Among those undergoing RBMT, 3 had a complete match, 2 a 1-locus mismatch, and 1 a 2-loci mismatch; in the RPBSCT subgroup, both patients had a 1-locus mismatch. All 4 patients receiving UBMT had a complete match. The conditioning regimen consisted of TBI in 20 patients, BU in 16, and other agents in 2. CSA and FK were used as GVHD prophylaxis in 20 and 18 patients, respectively (Table 4).

The 3-year posttransplantation EFS rate for all 38 patients undergoing HSCT was 54.4% (38.1%-70.7%) when the duration of EFS was calculated from the day of transplantation. For the 29 patients undergoing transplantation in first remission, it was 64.4% (46.4%-82.4%) compared with 22.2% (0%-49.4%) for the 9 patients undergoing transplantation in second remission or after relapse ($P = .0044$; Figure 4A). The difference in outcome between patients treated with HSCT in the 3- to 5-month window after diagnosis and those treated later in remission was not statistically significant. These results suggested that the timing of HSCT for infants with *MLL*$^+$ALL exerts a critical influence on outcome, prompting us to test this factor against other potentially important covariates. Stepwise multivariate analysis of posttransplantation EFS rates indicated independent predictive strength for remission status at HSCT (first remission versus other) in the context of age (younger versus older than 6 months at diagnosis), gender (male versus female), CNS invasion at diagnosis, initial WBC count (< 100 versus ≥ 100 × 10^9/L), and karyotype (4;11 translocation versus other; hazard ratio, 0.0268; $P < .0001$).

Patients undergoing UCBT in first remission tended to fare worse than those receiving other types of donor cells (3-year posttransplantation EFS rate, 58.7% versus 77.8%, $P = .3716$; Figure 4B), but the difference was not statistically significant; the numbers of patients in the RBMT, UBMT, and RPBSCT subgroups were too small to allow further comparisons. When the 20 patients with UCBT in first remission were stratified by HLA disparity, TBI and BU conditioning regimens, or CSA- and FK-based methods of GVHD prophylaxis, we found no significant differences in posttransplantation EFS, using Kaplan-Meier methods and log-rank test (data not shown). A repeated stepwise multivariate survival analysis, using the same risk factors as just described with the addition of HLA disparity (complete match versus 1-locus mismatch versus 2-loci mismatch), conditioning regimen (TBI versus BU), and method of GVHD prophylaxis (CSA versus FK), again demonstrated independent prognostic strength for time of HSCT (first remission versus other; hazard ratio, 0.2717; $P = .0226$).

Because it is possible that the patients undergoing HSCT in first remission had more favorable prognostic factors than others in the series, we compared selected clinical characteristics of these 2 groups. Apart from an older age at diagnosis for infants given transplants in first remission ($P = .0132$), there were no significant differences in gender, WBC count, time to transplantation, CNS invasion, and karyotype (data not shown).

Seven patients had relapses and one had graft failure following the first HSCT (Table 4). After subsequent UCBT (n = 2), RPBSCT (n = 1), or UBMT (n = 2), 3 infants undergoing UCBT or UBMT attained new CRs without further adverse events as of April 30, 2004. Consequently, 3 infants having relapses, including 2 undergoing HSCT in first remission and one in second remission, have been in CR after the second HSCT (Table 4).

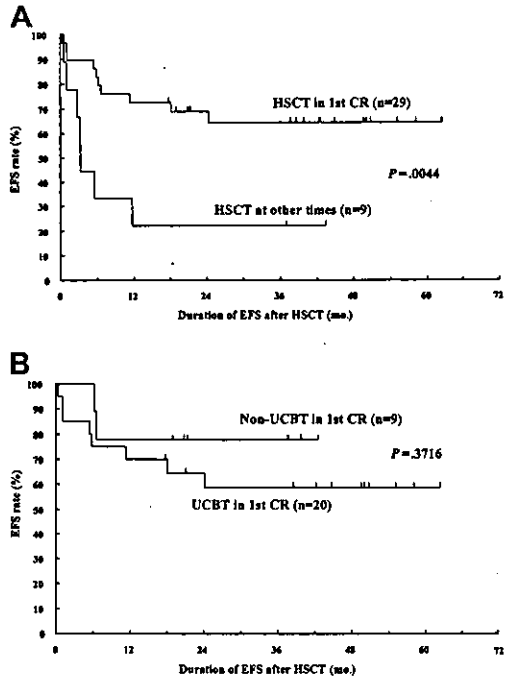

Figure 4. Comparison of EFS rates. Comparison of EFS rates for infants with *MLL*$^+$ ALL by remission status at the time of HSCT (A) and by the source of donor cells (B). Patients receiving transplants in first remission fared significantly better than those undergoing HSCT at other times (3-year posttransplantation EFS, 64.4% versus 22.2%, $P = .004$). There was no statistically appreciable difference in outcome between patients receiving cord blood or non–cord blood in first remission. Tick marks represent patients still at risk of death or other adverse events.

Toxicity

A major consideration in the treatment of ALL in infants is the significant potential for toxicity due to myeloablative chemotherapy and ionizing radiation. Two patients in our series died as a result of adenoviral infection or interstitial pneumonia during induction therapy. Fatal complications were not observed during the intensification phase of chemotherapy. Table 5 reports the toxicities associated with HSCT. Four patients had transplantation-related deaths due to sepsis, graft rejection, respiratory failure, or veno-occlusive disease of the liver (VOD)/thrombotic microangiopathy (TMA). Seven others, 5 of whom had undergone UCBT, developed grade II or III acute GVHD, whereas 3 others had chronic limited GVHD. Of the 7 patients presenting with VOD, 5 had received the BU-containing conditioning regimen. This complication was fatal in one infant and severe in another, who eventually required liver transplantation. Long-term side effects remain to be analyzed, although the late sequelae of the MLL96 protocol,[14] which relied on the same regimens used in MLL98, do not suggest any prohibitive complications. However, as preliminary results, growth impairment has been reported by several investigators who registered patients in this study undergoing HSCT with a TBI-conditioning regimen (E. I., unpublished observations, April 2004).

Discussion

Historically, the results of chemotherapy for infants with ALL, particularly those with 4;11 translocation/*MLL*$^+$or CD10$^-$ disease,

Table 5. Toxicities associated with HSCT

Deaths	No.
Total	14
Relapse	10
Transplantation-related death	4
Rejection	1
Sepsis	1
Respiratory failure	1
VOD/TMA	1
Complications	
Mucous membrane damage	19
VOD	7
Diarrhea/vomiting	5
Sepsis	5
Liver dysfunction	5
Interstitial pneumonia	3
Acute GVHD	14
Grade I	7
Grade II	5
Grade III	2
Chronic GVHD	3
TTP/TMA	3
Fungal infection	2
Rejection	2
Renal failure	1

TMA indicates thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

have been poor, with EFS rates ranging from 17% to 43%.[5,8,15-21] The best current results are those reported from the Dana-Farber Cancer Institute, where an intensified drug regimen yielded a 4-year EFS rate of 54% in all infants with ALL and 43% in those with *MLL*$^+$ disease; however, the patient sample was too small to permit firm conclusions.[22] Considered together, these findings suggest that the outcome for *MLL*$^+$ infant ALL is unlikely to be improved with use of intensive chemotherapy alone. This interpretation is supported by the experience in Japan. Between 1996 and 1998, we treated infant ALL according to the presence (HSCT) or absence (intensive chemotherapy only) of *MLL* gene rearrangements, securing a 3-year EFS rate of 34.0% for *MLL*$^+$ cases, which did not represent an improvement over previous reports.[14] Most of these patients had relapses within 6 months after the initiation of chemotherapy; however, the 3-year posttransplantation EFS rate for *MLL*$^+$ patients undergoing HSCT in first remission was 58.0%, suggesting a therapeutic advantage for early use of transplantation.[14]

Thus, in the current study, we elected to initiate HSCT within 3 to 5 months after diagnosis as a means to reduce the relapse rate in infants with *MLL*$^+$ALL who had achieved remission. The 3-year postdiagnosis EFS rate for these patients increased to 43.6%, but the gain over our previous experience was not statistically significant.[14] Nonetheless, the relatively high 3-year posttransplantation EFS rate for patients undergoing HSCT in first remission (64.4%) is encouraging and supports the working hypothesis of MLL98. Failure to produce a significant improvement over the postdiagnosis HSCT results in MLL96 can be attributed, in part, to the dismal prognosis of infants with CNS invasion or age younger than 6 months, many of whom had a disease relapse before HSCT could be attempted. Clearly, the development of more effective induction and intensification therapies for these subgroups should be a priority of future investigations.

Marco et al[13] performed allogeneic or autologous HSCT in 26 patients with infant leukemia, including AML. They noted that patients given transplants earlier than 4 months after remission induction had a significantly better prognosis than those undergoing the procedure at later times. Moreover, the period from remission induction to transplantation was the sole prognostic factor identified by multivariate analysis. Similarly, Leung et al[23] studied 22 infant leukemia patients treated with HSCT, reporting that disease status at transplantation was the only prognostic factor with significant predictive strength in patients in remission. These findings, together with our similar result by multivariate analysis, suggest that the early introduction of HSCT could save a proportion of patients who otherwise would have relapses relatively soon after induction therapy. On the other hand, Pui et al[9] evaluated a substantial number of childhood ALL patients presenting with 11q23 abnormalities and concluded that HSCT was not effective in this series. In this retrospective analysis, however, the treatment method, source of donor cells, and conditioning regimen varied widely among the patients. In particular, the EFS rate for infants was too low (only 19%) to permit an accurate assessment of the effect of HSCT, in contrast to our MLL98 study, in which all *MLL*$^+$ cases were assigned to the HSCT arm.

The majority of patients in the current investigation underwent UCBT rather than UBMT, for the following reasons. First, cord blood can be obtained within 2 months from donors in Japan, whereas it usually takes 5 to 6 months to identify a suitable unrelated marrow donor through the Japan Marrow Donor Program (JMDP) and proceed to transplantation. Second, cord blood can provide sufficient numbers of donor cells for patients with a low body weight, such as infants. Third, a nationwide network of cord blood banks has been established in Japan (approximately 16 000 cord blood units had been stored as of October 2003), permitting the procurement of adequate quantities of cord blood mismatched at 2 or fewer loci in nearly all cases.[24-26] Fourth, cord blood transplants are associated with a relatively low risk of GVHD,[26-30] although this benefit may be offset by a diminished graft-versus-leukemia (GVL) effect and a higher risk of relapse.[31] In our study, the EFS of patients undergoing UCBT tended to be lower than that associated with other sources of donor cells. Thus, in future studies, the induction of GVL reactions using ubenimex or granulocyte-macrophage colony-stimulating factor (GM-CSF) should be considered as a means to prevent relapse.[32,33]

Two patients who underwent UCBT following treatment with the BU-containing regimen had complications associated with graft rejection. Although the pharmacokinetics of BU in infants are unknown, the absorption and metabolism of oral BU vary widely among individual patients,[34-36] indicating a need to develop an effective BU pharmacokinetics monitoring system for younger children.[37] In addition, the incidence of VOD was higher than in previous reports on the outcome of HSCT in infants, despite the administration of ursodeoxycholic acid and heparin to most patients in this investigation. The factors contributing to this unexpectedly high frequency of VOD remain unclear, and this issue must be addressed in the future.

A major concern with the use of HSCT in infants is the possibility of late adverse sequelae, including growth impairment. Pirich et al[12] performed allogeneic HSCT in 7 infants with ALL using a conditioning regimen that incorporated TBI, CPA, and VP-16; this protocol contributed to short stature in 3 patients, with TBI implicated as the principal risk factor.[38] TBI was also reported to be a risk factor for hypopituitarism and cataract, and these toxicities were inversely correlated with age.[13,39] We analyzed growth and development in 34 infants with ALL followed for 5 to 8 years who had been treated on MLL96 protocol,[14] which included intensive chemotherapy and HSCT administered in much the same way as in the MLL98 study. Growth (body height and body weight)

was compared by analysis of variance among patients receiving chemotherapy alone (chemotherapy group, n = 19), HSCT with a TBI-conditioning regimen (TBI group, n = 9), and HSCT with a BU-conditioning regimen (BU group, n = 6) at the onset of leukemia, at the time of treatment cessation, and at 1, 2, and 3 years after treatment. At 3 years after the completion of therapy, patients in the TBI group showed marked growth impairment (mean body height, −2.2 SD; mean body weight, −0.9 SD) that tended to be more pronounced but not significantly different from results in the chemotherapy (−0.3 SD; +0.3 SD) and BU (−1.2 SD; −0.6 SD) groups ($P = .063$ and $P = .071$, respectively). As for other late sequelae, psychosomatic deterioration was observed in 3 patients (1 in the BU and 2 in the chemotherapy groups), hypothyroidism in one TBI-treated patient, and immunodeficiency in one patient receiving chemotherapy only. Neither lung nor cardiac dysfunctions nor second malignancies were detected in any patient in this series. These findings support the recommendation that TBI be eliminated from future studies of HSCT in infants with *MLL*$^+$ALL, particularly in view of the similar EFS rates for the TBI- and BU-treated subgroups.

Recently, reduced-intensity hematopoietic stem cell transplantation (RIST) using nonmyeloablative conditioning has become available for leukemia patients.[40,41] Because the effects of HSCT are partly attributable to an antileukemic immune reaction mediated by donor lymphocytes, the aim of RIST is to promote a GVL effect, thus contributing to an improved survival rate and fewer transplant-related complications. Recent reports indicate that RIST could be effective for high-risk ALL[42] or non-Hodgkin lymphoma.[43,44] Barker et al[45] also performed UCBT with RIST in adults, obtaining a high engraftment rate and satisfactory end results. Another report noted that an infant with AML survived free of disease despite episodes of grade II GVHD following UCBT with RIST.[46] Consequently, RIST may replace conventional myeloablative HSCT for infants with *MLL*$^+$ALL, especially those who are ineligible for high-dose chemoradiotherapy because of immature organs or the risk of late toxicities. However, the number of infants who have received RIST is too small to allow definite recommendations.

Although the present investigation tested HSCT in all infants with *MLL*$^+$ALL, it may be possible to identify subgroups that would fare well without transplantation. The Berlin-Frankfurt-Munster (BFM) group,[7] for example, reported that the early response to prednisone was the strongest prognostic factor in infant ALL, so that poor responders to this agent may be the only group requiring HSCT in first remission. Two large cooperative groups (Children's Oncology Group and Interfant) initiated international studies to test the efficacy of intensified chemotherapy for infant ALL. A preliminary study by the Children's Oncology Group yielded a 2-year EFS rate of 60% in infants with *MLL*$^+$ALL[47]; results of the Interfant99 study have not yet been published, although initial analyses indicate an improvement in outcome. Thus, a major challenge for the future will be to confirm the efficacy of intensified chemotherapy for selected subgroup of infants. Recently, the level of minimal residual disease (MRD) has emerged as a powerful prognostic factor in childhood ALL. In patients with t(4;11)$^+$ ALL, the detection of MRD with the polymerase chain reaction (PCR) was significantly related to outcome.[48] Indeed, in our preliminary study, MRD was present after induction or intensification chemotherapy in most *MLL*$^+$ patients (unpublished data, November 2003). Hence, monitoring of MRD by PCR should be considered as an additional means to discriminate among subgroups with a favorable or unfavorable prognosis.

This investigation suggests that the early introduction of HSCT, preferably within 3 to 5 months after diagnosis, can be an effective strategy in terms of preventing relapse in infants with *MLL*$^+$ ALL. Two subgroups in our study, patients younger than 6 months with high WBC counts ($\geq 100 \times 10^9$/L) and those with CNS invasion at diagnosis, continued to fare poorly, indicating a need to consider more frequent intrathecal chemotherapy or intensified high-dose Ara-C therapy before HSCT for these patients. For all infants undergoing HSCT, less toxic conditioning regimens might be introduced without any appreciable loss of efficacy. Finally, the identification of subgroups who may respond well to intensified chemotherapy alone should be given a high priority in future investigations.

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Appendix

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