厚生労働科学研究費補助金
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若年者骨髄性造血器腫瘍を対象とした骨髄破壊的前処置と骨髄非破壊的前処置を用いた同種末梢血幹細胞移植の比較的検討（第Ⅲ相ランダム化盲検比較試験）（H16－がん臨床－019）

平成15年度～平成17年度　総合研究報告書

主任研究者　谷　口　修　一

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目　　次

Ⅰ．総合研究報告

厚生労働科学研究費補助金　がん臨床研究事業

総合研究報告書

『若年者骨髄性造血器腫瘍を対象とした骨髄破壊的前処置と骨髄非破壊的前処置を用いた同種末梢血幹細胞移植の比較的検討（第Ⅲ相ランダム化盲検比較試験）』

主任研究者　谷口　修一　国家公務員共済組合連合会　虎の門病院　血液科　部長

研究要旨：

ミニ移植は、同種移植の高い非再発率が同種免疫反応による抗腫瘍効果が主体であるという考え方に基づいて、移植前治療は移植を成立させるだけの免疫抑制治療にとどめるものである。ミニ移植の登場により、従来型移植法では実施不可能であった高齢者や臓器障害を持つ症例にも広く同種移植の機会を提供し、既にその高い安全性と有効性が報告され、ミニ移植数は国内外とも飛躍的に増加している。しかし、十分移植前に抗がん治療を行う従来型移植前処置法との比較試験は実施されておらず、その正確な比較はできていない。よって従来型の移植もミニ移植もどちらも実施可能な若い年齢層で比較検討を行う必要があった。しかし、若年者に応用するに当たり 55 歳以下の年齢層では従来型移植が標準治療として行われており、臨床第Ⅲ層比較試験の症例数確保は困難と考えられた。そこで、ミニ移植の最大の特徴である移植後早期の QOL が維持される点、またそれに伴い移植後の平均の生存期間がミニ移植の方が長くなる点に着目し、QOL-adjusted life year(QALY)を主要評価項目とすることにより、必要な症例数を確保することとした。しかし同種移植領域における適切な QOL 評価法がいまだ存在せず、当研究班において移植前後の毒性から、特に移植後中後期の QOL に大きく寄与すると思われる移植片宿主病(GVHD)まで視野に入れた QOL 評価法を確立する臨床試験をおこなった。また、ミニ移植における標準的な移植前処置法も確立されていないことも問題となった。標準的前処置とされるブスルファン(BU)＋シクロフォスファミド(CY)から BU の量は軽減せず、主に宿主の免疫抑制に働き、拒絶予防として使用されている CY を、より安全性の高いフルダラビン(Flu)に変更する移植前処置による臨床試験を 20-65 歳と言う幅広い年齢層に施行し、その成績を評価することとした。

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A．研究目的

同種造血幹細胞移植は白血病などの難治性造血器悪性腫瘍に対する根治的な治療として行われてきた。従来型の同種移植は腫瘍細胞を絶滅させる目的にて、移植前に超大量の放射線や抗がん剤を投与するため(骨髄破壊的前処置、フル移植)、それに耐えうる臓器機能が維持された症例(通常55歳以下)だけがその対象であった。ミニ移植は、同種移植の低い非再発率ひいては高い長期生存率は同種免疫反応による抗腫瘍効果が主体であるという考え方に基づいて(graft versus leukemia 効果；GVL 効果)、移植前治療は移植を成立させる目的だけの免疫抑制治療にとどめている(骨髄非破壊的前処置)。ミニ移植の登場により、従来型移植ではその対象となりえなかった高齢者や臓器障害を持つ症例にも広く同種移植を受ける機会を提供し、既にその高い安全性と有効性が報告され、ミニ移植数は国内外とも飛躍的に増加している。次の段階として高齢者にミニ移植がフル移植と同等であるならば、若年者でも前処置関連毒性の強いフル移植を受ける必要はないことが予想される。この仮説を検証するため、50 歳未満の若年者に対するフル移植とミニ移植を比較する多施設共同第Ⅲ相試験を企画した。初年度(2003 年度)は、分担研究者を含む可能な限り幅広く全国の移植施設の医師からなるプロトコール検討会を実施した。ミニ移植の概念は、1995 年頃から欧米を中心に特に低悪性度群のろ胞性リンパ腫など腫瘍の増殖速度が遅く、ドナーリンパ球輸注などの移植後の GVL 効果が期待できる症例を中心に発展してきた。国内では、移植前処置で Flu は健保適応外となるためその発展が遅れて、施設間や地域間でミニ移植の適応に対するかなりの温度差があることが判明した。よってフル移植が可能な若い世代での全国多施設共同第Ⅲ相試験が実施不能で、加えてミニ移植における標準的な移植前処置法も確立されていないことから、臨床第Ⅰ-Ⅱ相を実施し、適切な移植前処置法を確立せねばならない状況であることが判明した。よってミニ移植のより安全で有効な移植前治療法を確立する目的にて、全国の移植医の中でコンセンサスが得られやすい大量の CY の代わりに Flu を使用する Flu+BU 16mg/kg の臨床試験を開始する。

またミニ移植の最大の特徴である移植後早期の QOL が維持される点、またそれに伴い少なくとも移植後短期的な生存期間がミニ移植の方が長くなる点に着目し、QOL-adjusted life year(QALY)を主要評価項目とすることを考えた。しかし同種移植領域における移植前後の毒性から、特に移植後中後期の慢性 GVHD や二次的免疫不全に伴う極めて複雑な臨床経過全体を把握するような適切な QOL 評価法がないことも明らかとなり、当研究班において QOL に大きく寄与すると思われる移植片宿主病(GVHD)まで視野に入れた QOL 評価法を確立する臨床試験をおこなう必要があった。

この二つの臨床試験の後に QALY を主要評価項目とする第Ⅲ相試験を行う。

B．研究方法

QOL 評価：　被験者に対し、QOL 評価尺度として既に利用可能な自記式調査票（SF-36, EQ-5D, FACT-BMT)の日本語版を用いた QOL 調査、Time-trade off 法を用いたインタビューによる QOL 調査を行う。被験者への QOL 調査の回答に要した時間、QOL 調査負担感、回答の欠損理由などに関する調査も行う。またこの調査は担当医師・看護師などの医療者とは異なる立場のインタビュアーにより行われる。これと平行して、被験者の医学的・臨床的情報を収集する為、医師・医療従事者への調査票による情報収集を行う。目標症例はフル移植 10 例、ミニ移植 10 例とし、QOL 評価法の妥当性を検討する。

Flu/BU 臨床試験：また Flu/BU の前処置によるミニ移植の臨床試験は、対象症例は年齢が 16 歳以上かつ 65 歳以下の同種造血幹細胞移植が通常適応となる造血器疾患患者で、HLA の A/B/DR 座が完全一致した同胞または血縁ドナー、または HLA-A/B/DR 遺伝子型

6/6 一致非血縁ドナーもしくは HLA-A/B 遺伝子型一致 DRB1 遺伝子型 1 座不一致非血縁ドナーを有するものとする。主要評価項目は移植後 100 日の時点での生着生存率に設定した。本臨床研究の目的は、Flu/BU による骨髄破壊的な移植前処置による同種移植により、前処置関連毒性が軽減されること、かつ生着が遅延しないことおよび再発が増加しないことを確認することである。具体的な対象疾患は、非寛解例を除く急性白血病、急性転化期を除く慢性骨髄性白血病、白血病に転化していない骨髄異形成症候群の症例とする。

倫理上の問題点に対する配慮

本研究は、適格基準と除外基準より適格と判断される症例に対し、本療法の有効性と危険性について十分な説明を行い、同意が得られた者についてのみ施行した。

C．研究結果

QOL 評価研究は、既に研究計画書は完成し、平成 17 年度に国立がんセンター、東大病院、都立駒込病院、虎の門病院で本研究計画書を倫理委員会に提出した。倫理委員会を通過した虎の門病院において既に 4 例が登録され、臨床試験続行中である。平成 17 年度で研究班が終了したため、これ以上の登録はなかった。ただ、移植前処置開始後から移植後血球回復の時期までは抗がん剤や放射線照射による嘔気、嘔吐、著明な倦怠感、下痢などの毒性、白血球減少に伴う感染症、GVHD による下痢、皮疹、肝障害などが高頻度に出現する時期でもあり、この次期でのインタビュアーによるヒアリングは全例での実施は困難であった。

Flu/BU の前処置については。虎の門病院と国立がんセンター中央病院との 2 施設共同研究として、倫理委員会にて申請する段階である。これも、研究班終了とともに臨床研究としては実施できなかったが、既に practice として幅広く行われており、臨床試験企画の妥当性が証明された。

D．考察

ミニ移植の若年者への応用に伴い多くの問題点が浮上した。具体的には、1)移植前処置を軽減することで再発が増加する可能性、2)臓器機能が維持されている若年者においては多くの症例で BU/CY や全身放射線照射+CY 等の骨髄破壊的移植は安全に施行できる(ミニ移植を応用する必要がない)、3)そもそもミニ移植の具体的方法論が確立していない、などの問題点である。しかし、これらの大量の放射線照射や抗がん剤投与が移植関連死亡へ繋がる症例も確実に存在し(5-20%)、長期的にも成長障害、内分泌異常、不妊、2 次発ガンなどの問題へ発展していることも明らかである。また、これらの標準的移植前処置法も決して臨床第Ⅲ相試験を経て確立した標準的治療ではなく臨床Ⅱ相的な臨床試験を経て同種造血幹細胞移植が世界に普及すると共に標準とされているものであり、エビデンスとして耐えられる臨床Ⅲ相的臨床試験は存在しないのも現状である。

ただ国内において前記の理由にて少なくともフル移植が施行可能な若い世代で比較試験を行うのは困難であった。よって、BU の投与を減量せず抗腫瘍効果は損なわないが、主に宿主の免疫を抑制し拒絶予防として使用されている毒性が強い CY をより安全に投与可能な Flu に変更する Flu/BU の臨床試験を 20-65 歳と言う幅広い年齢層に施行し、まずその成績を評価することは重要と考えた。単に CY を Flu に替えるだけでも移植前処置の安全性は高まり、抗腫瘍効果を担保する BU 投与量は変更しておらず、単に至適なミニ移植の前処置の開発にとどまらず、今後の移植医療の標準的前処置に置き換わる可能性がある。

QALY は長期的にも慢性 GVHD や 2 時的な免疫不全に伴うさまざまな合併症を来す移植医療においては極めて重要な評価法である。移植後早期(1-2 ヶ月まで)の評価法については、今後に課題を残したが、特に長期生存例でのさまざまな視点からの QOL 評価については同種移植医療に欠かせないものであり、標準的な評価法の確立は急務である。

E．結論

CY の毒性を回避するために、より安全に投与可能な Flu に変更し、抗腫瘍効果の主体である BU は減量

しない若年者も含めた年齢層でのFlu/BU16による前処置を評価する臨床試験計画書を完成させ、臨床試験を開始する。同種造血幹細胞移植領域におけるQOL評価法を確立する臨床試験を行った。

F．健康危険情報

該当なし

G．研究発表

総括報告書、分担報告書に準ずる。

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅲ. 研究成果の刊行物・別刷

Featured Article

Successful Engraftment After Reduced-Intensity Umbilical Cord Blood Transplantation for Adult Patients with Advanced Hematological Diseases

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ABSTRACT

Purpose: **The purpose of this research was to evaluate the feasibility of reduced-intensity unrelated cord-blood transplantation (RI-UCBT) in adult patients with advanced hematological diseases.**

Experimental Design: **Thirty patients (median age, 58.5 years; range, 20–70 years) with advanced hematological diseases underwent RI-UCBT at Toranomon Hospital between September 2002 and August 2003. Preparative regimen composed of fludarabine 25 mg/m^2 on days −7 to −3, melphalan 80 mg/m^2 on day −2, and 4 Gy total body irradiation on day −1. Graft-*versus*-host disease prophylaxis was composed of cyclosporin alone.**

Results: **Twenty-six patients achieved primary neutrophil engraftment after a median of 17.5 days. Median infused total cell dose was 3.1 × 10^7/kg (range, 2.0–4.3 × 10^7/kg). Two transplant-related mortalities occurred within 28 days of transplant, and another 2 patients displayed primary graft failure. Cumulative incidence of complete donor chimerism at day 60 was 93%. Grade II-IV acute graft-*versus*-host disease occurred in 27% of patients, with median onset 36 days. Primary disease recurred in 3 patients, and transplant-related mortality within 100 days was 27%. Estimated 1-year overall survival was 32.7%. Excluding 7 patients with documented infection, 19 patients displayed noninfectious fever before engraftment (median onset, day 9). Manifestations included high-grade fever, eruption, and diarrhea. The symptoms responded well to corticosteroid treatments in 7 of 13 treated patients.**

Conclusion: **This study demonstrated the feasibility of RI-UCBT in adults.**

INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a curative treatment for refractory hematological malignancies. The therapeutic benefits are attributable to myeloablative radiochemotherapy and graft-*versus*-leukemia effects (1), whereas the severe regimen-related toxicity (RRT; Ref. 2) limited allo-HSCT to young patients without comorbidities.

Reduced-intensity stem-cell transplantation (RIST) using a nonmyeloablative preparative regimen has been developed to decrease RRT, whereas preserving adequate antitumor effects (3–5). Different pioneering conditioning regimens for RIST have been investigated, such as those including purine analogs (3–6) and total body irradiation (TBI). Although RIST has been attempted in various diseases (5, 6), suitable preparative regimens with adequate immunosuppression have yet to be established.

Although allo-HSCT from an HLA-identical sibling is promising, only 30% of the patients have an HLA-identical sibling donor. The value of unrelated cord-blood transplantation (UCBT) was confirmed for pediatric patients (7, 8). It has seen recent application in adult patients (9). Whereas the potential graft-*versus*-leukemia effects by cord-blood (CB) without severe graft-*versus*-host disease (GVHD; Ref. 10) has been reported, current questions include whether CB provides a sufficient number of stem cells for adults and suitable graft-*versus*-leukemia effects.

Reduced-intensity (RI)-UCBT (11, 12) represents a promising treatment for advanced hematological malignancies. Wagner *et al.* (12) reported recently the feasibility of RI-UCBT for pediatric patients. However, the feasibility in adult patients remains unclear. We report 30 adult patients with advanced hematological diseases who underwent RI-UCBT after fludarabine, melphalan, and 4 Gy TBI since October 2003 at our institution.

PATIENTS AND METHODS

Study Patients and Donors. Thirty patients with hematological diseases underwent RI-UCBT at Toranomon Hospital between September 2002 and August 2003. All of the patients had hematological disorders that were incurable with conventional treatments and were considered inappropriate for conven-

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tional allo-HSCT due to the lack of an HLA-identical sibling or a suitable unrelated donor, age >50 years old and/or organ dysfunction (generally attributable to previous intense chemo- and/or radiotherapy).

All of the patients provided written informed consent in accordance with the requirements of the Institutional Review Board.

HLA Typing and Donor Matching. An unrelated donor was searched through the Japan Marrow Donation Program (13) for patients without an HLA-identical sibling donor. When no appropriate donor was identified, the Japan Cord Blood Bank Network (14) was searched. CB units, which were ≥4 of 6 HLA-antigen matched and contained at least 2×10^7 nucleated cells/kg of recipient body weight before freezing were used. CB units were not depleted of T lymphocytes.

Preparative Regimen. The preparative regimen was composed of fludarabine 25 mg/m^2 on days −7 to −3, melphalan 80 mg/m^2 on day −2, and 4 Gy TBI in 2 fractions on day −1.

Supportive Cares. All of the patients were managed in reverse isolation in laminar airflow-equipped rooms and received trimethoprim/sulfamethoxazole for *Pneumocystis carinii* prophylaxis. Fluoroquinolone and fluconazole were administered for prophylaxis of bacterial and fungal infections, respectively. Prophylaxis of herpes virus infection with acyclovir was also given (15). Neutropenic fever was managed according to the guidelines (16, 17). Cytomegalovirus (CMV) pp65 antigenemia was monitored once a week. If positive results were identified, preemptive therapy with foscarnet was initiated. Hemoglobin and platelet counts were maintained at >7 g/dl and $>10 \times 10^9$/liter, respectively, with in-line filtered and irradiated blood transfusions.

Management of GVHD. GVHD was clinically diagnosed in combination with skin or gut biopsies after engraftment or attainment of 100% donor chimerism. Acute and chronic GVHD were graded according to the established criteria (18, 19).

GVHD prophylaxis was a continuous infusion of cyclosporin 3 mg/kg from day −1 until the patients tolerated oral administration. It was tapered off from day 100 until day 150. If grade II-IV acute GVHD developed, 1 mg/kg/day of prednisolone was added to cyclosporin and tapered from the beginning of clinical response.

Chimerism Analysis. Chimerism was assessed using fluorescent *in situ* hybridization in sex-mismatched donor-recipient pairs. In sex-matched pairs, PCR for variable numbers of tandem repeats was used with donor cells detected at a sensitivity of 10% (20).

Whole blood and CD3-positive cell chimerism was assessed at the time of granulocyte engraftment. When engraftment was delayed, chimerism was assessed on day 30. For those who died before engraftment, chimerism was assessed at least once during life.

Engraftment. Engraftment was defined as WBC counts $> 1.0 \times 10^9$/liter or absolute neutrophil counts $> 0.5 \times 10^9$/liter for 2 consecutive days. Granulocyte colony stimulating factor (Filgrastim) 300 μg/m^2/day was administered i.v. from day 1 until neutrophil engraftment.

Graft failure was defined as peripheral cytopenia and marrow hypoplasia occurring later than day 60, without detection of donor markers by cytogenetic and/or molecular techniques.

Table 1 Patient characteristics (n = 30)

Age (y), median (range)	58.5 (20–70)
Weight (kg), median (range)	52 (38–75)
Male/female	16/14
Diagnosis	
Malignancy	
Acute myeloid leukemia	14
Myelodisplastic syndrome	1
Acute lymphoblastic leukemia	3
Adult T-cell leukemia	5
Plasma cell leukemia	1
Chronic myeloid leukemia	1
Malignant lymphoma	1
Benign	
Severe aplastic anemia	4
Disease status at transplantation (malignancy)	
Remission	1
Refractory to previous chemotherapy	25

RRT and Transplantation-Related Mortality (TRM). RRT was defined as any nonhematological organ dysfunction from day 0 to day 28 and was graded according to the Bearman's criteria (2). TRM was defined as death without the primary disease progression.

Endpoints and Statistical Analysis. Primary end points were composed of the rates of durable engraftment and TRM within day 100. Secondary end points were the rates of RRT, acute and chronic GVHD, infections, event-free survival (EFS), and overall survival (OS).

Acute GVHD was analyzed for engrafted patients. Chronic GVHD was analyzed for patients who survived ≥100 days.

EFS was defined as the duration of survival after transplantation without disease progression, relapse, graft failure, or death. The probabilities of OS and EFS were shown by the Kaplan-Meier method as of January 31, 2004. Surviving patients were censored on the last day of follow-up. Cox regression analysis was used to determine the effect of various variables on OS.

RESULTS

Patient Characteristics. Median age was 58.5 years (range, 20–70 years), and median weight was 52 kg (range, 38–75 kg; Table 1). All of the patients were CMV-seropositive.

The malignancies of 25 patients were refractory to cytotoxic chemotherapies except acute myeloblastic leukemia (n = 1) in first CR. The remaining 4 patients had transfusion-dependent severe aplastic anemia.

CB Characteristics. Twenty-four and 6 patients received 4 of 6 and 5 of 6 HLA-antigen-matched CB, respectively. Twenty-one patient CB pairs were sex-mismatched. Median infused total nucleated cell dose and CD34-positive cell dose before freezing were 3.1×10^7/kg (range, $2.0–4.3 \times 10^7$/kg) and 0.74×10^5/kg (range, $0.17–2.5 \times 10^5$/kg), respectively.

Engraftment. Twenty-six patients [87%; 95% confidence interval (95% CI), 75–99%] achieved primary neutrophil engraftment, among whom median day of engraftment was 17.5 days (range, 10–54 days; Fig. 1). Their engraftment was durable

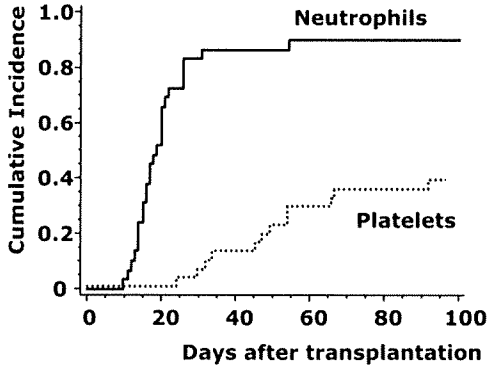

Fig. 1 Engraftment of neutrophils and platelets. Twenty-six (87%; 95% confidence interval, 75–99%) and 16 patients (40%; 95% confidence interval, 25–57%) achieved primary neutrophil and platelet engraftment, respectively.

Table 2 Neutrophil engraftment, chimerism, and overall survival

Neutrophil engraftment Variable	n	% (95% CI)[a]	*P*
Total cell dose			
≧3 × 10^7/kg	16	94% (82–100%)	
<3 × 10^7/kg	14	79% (57–100%)	0.25
HLA disparities			
HLA 5/6 match	6	67% (29–100%)	
HLA 4/6 match	24	92% (81–100%)	0.24
100% Donor chimerism			
Total cell dose			
≧3 × 10^7/kg	16	100%	
<3 × 10^7/kg	14	86% (67–100%)	0.63
HLA disparity			
HLA 5/6 match	6	83% (54–100%)	
HLA 4/6 match	24	96% (88–100%)	0.31
Overall survival			
Total cell dose			
≧3 × 10^7/kg	16	54% (24–83%)	
<3 × 10^7/kg	14	52% (6.6–87%)	0.70
HLA disparities			
HLA 5/6 match	6	63% (20–100%)	
HLA 4/6 match	24	51% (20–81%)	0.60

[a] CI, confidence interval.

without requiring readministration of Filgrastim. Two patients died of TRM within 28 days of transplant. Primary graft failure occurred in the remaining 2 patients, who underwent second RI-UCBT with the same preparative regimen and GVHD prophylaxis and achieved neutrophil engraftment and complete donor chimerism. No patients experienced a decrease in neutrophil <0.5 × 10^9/liter during the follow-up.

Platelet counts >20 × 10^9/liter were achieved by 16 patients (40%; 95% CI, 25–57%) on a median day of 39 days (range, 25–95 days). No other patient achieved platelet recovery until the last day of follow-up.

No significant association was found between neutrophil engraftment and either infused cell dose or HLA disparity (Table 2).

Chimerism Analysis. Chimerism data were obtained from all of the 30 patients. Cumulative incidence of complete donor chimerism at day 60 was 93% (95% CI, 84–100%), and median time to complete donor chimerism was 22 days (range, 13–56 days; Fig. 2). The 2 patients who died of TRM within 28 days had complete donor chimerism before neutrophil engraftment. All of the surviving patients were monitored for chimerism every 3 months, followed the cyclosporine tapering schedule from day 100 to day 150, and maintained complete donor chimerism during the follow-up even after the discontinuation of immunosuppressants.

No significant association was identified between complete donor chimerism and either infused cell dose or HLA disparity (Table 2).

RRT and TRM. Four patients (13%) developed grade III RRT. No patient had grade IV RRT. The most commonly involved organs were the gut and kidney (Table 3).

TRM within 100 days of RI-UCBT was 27%. Primary causes of death were interstitial pneumonitis (n = 2), acute GVHD (n = 2), gastrointestinal bleeding (n = 1), acute heart failure (n = 1), limbic encephalopathy (n = 1), and sepsis (n = 1).

GVHD. Grade II-IV and III-IV acute GVHD occurred in 27% (95% CI, 11–43%) and 23% (95% CI, 7.4–39%) of the patients, respectively. Median onset of grade II-IV acute GVHD was day 36 (range, day 17–66; Fig. 3).

Of the 13 patients who survived >100 days, 3 (23%) developed chronic GVHD.

Infection. Twelve patients developed infections: bacteremia (n = 8), invasive aspergillosis (n = 3), and pulmonary tuberculosis (n = 1). Nine of them had been treated with

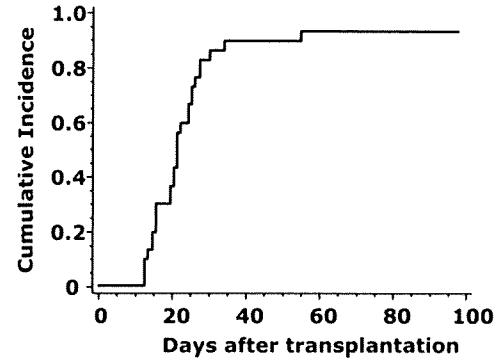

Fig. 2 Achievement of complete donor chimerism. Cumulative incidence of complete donor chimerism at day 60 after reduced-intensity unrelated cord-blood transplantation (*RI-UCBT*) was 93% (95% confidence interval, 84–100%), and median time to complete donor chimerism was day 22 (range, day 13–56).

Table 3 Regimen-related toxicity within 28 days (Bearman's score)

Score	Diarrhea	Kidney	CNS[a]	Liver	Lung
Grade 0	18	18	26	22	27
Grade 1	8	5	0	3	2
Grade 2	4	6	1	4	0
Grade 3	0	1	3	1	1
Grade 4	0	0	0	0	0

[a] CNS, central nervous system.

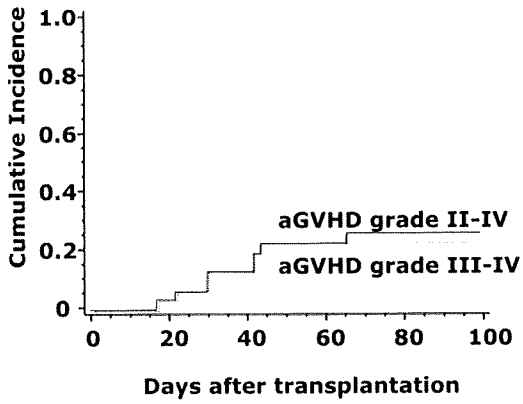

Fig. 3 Development of acute graft-*versus*-host disease (GVHD). Grade II-IV and III-IV acute GVHD developed in 27% (95% confidence interval, 11–43%) and 23% (95% confidence interval, 7.4–39%) of the patients, respectively. Median onsets of grade II-IV and III-IV acute GVHD were day 36 (range, day 17–66) and day 30 (range, day17–44), respectively.

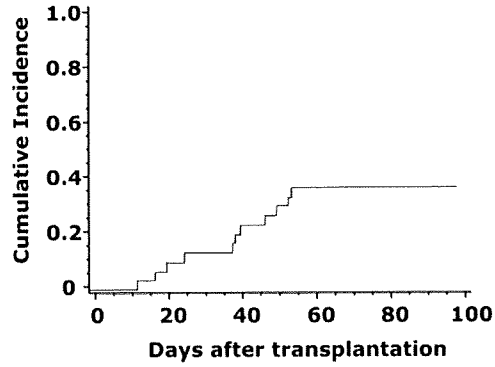

Fig. 4 Development of cytomegalovirus reactivation. Reactivation of cytomegalovirus was documented in 11 patients (37%) on a median of day 40 (range, day 13–55).

corticosteroids at the onset of infections. Reactivation of CMV was documented in 11 patients (37%) on a median of day 40 (range, day 13–55; Fig. 4). Eight of them had been treated with corticosteroids at the onset of CMV antigenemia. None of them developed CMV-related diseases. One patient developed hemorrhagic cystitis with adenovirus and BK virus infection.

Pre-Engraftment Noninfectious Fever. Seven patients with documented infection before engraftment were excluded from the analysis of pre-engraftment reaction (Table 4). Eighteen patients developed noninfectious fever before neutrophil engraftment (Fig. 5). Noninfectious high-grade fever often coexisted with eruption, diarrhea, and weight gain, starting on a median of day 9. Pathological examination of eruption from 8 patients revealed nonspecific inflammatory reactions and was not compatible with GVHD.

Survival. As of January 2004, a total of 11 patients remained alive. Median follow-up of the survivors and all of the enrolled patients were 238 days (range, 169–485) and 125 days (range, 26–485), respectively. Primary diseases recurred in 3 patients. Estimated 1-year OS and EFS were 32.7% (95% CI, 14.3–51.1%; Fig. 6) and 22.2% (95% CI, 5.9–38.5%; Fig. 7), respectively. Neither cell dose nor HLA disparity was associated with OS (Table 2).

DISCUSSION

Because CB contains a small amount of hematopoietic stem cells and stem cell boost or donor lymphocyte infusion is not available after UCBT, graft failure has been a major concern in adult UCBT. The present study demonstrated the feasibility of RI-UCBT for adult patients, in addition to pediatric patients (21). In this study, 26 of the 30 patients (87%) achieved durable engraftment, and 28 patients achieved complete donor chimerism by day 60, including 2 patients who died before engraftment. Interestingly, 4 patients with severe aplastic anemia, which has been associated with a high incidence of graft rejection (22), achieved complete chimerism after our reduced-intensity regimen. These findings suggest that the combination of fludarabine, melphalan, and low-dose TBI might be more immunosuppressive than conventional myeloablative regimens, creating niche for CB to engraft. Alternatively, CB may exert a strong graft-*versus*-host effect, making room for stable engraftment of stem cells.

Delayed hematopoietic recovery and infection during neutropenia are the significant concerns in adult UCBT. Laughlin *et*

Table 4 Characteristics of pre-engraftment reaction (n = 23)

Temperature	
38.0–38.9°C	2
39.0–39.9°C	10
≥40.0°C	7
Day of peak body temperature	9 (5–12)
Serum levels of CRP[a] (mg/dl)	13.8 (0.5–18.9)
Day of peak serum levels of CRP	10 (8–16)
Diarrhea	11
Eruption	10
Jaundice	5
Use of corticosteroid	13
Good response to corticosteroid	7

[a] CRP, C-reactive protein.

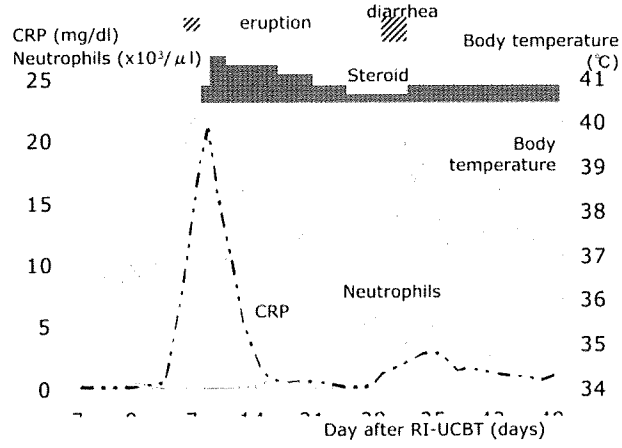

Fig. 5 Clinical course of a patient who developed pre-engraftment fever. Immune-reactions display two peaks, at around day 9 and day 18.

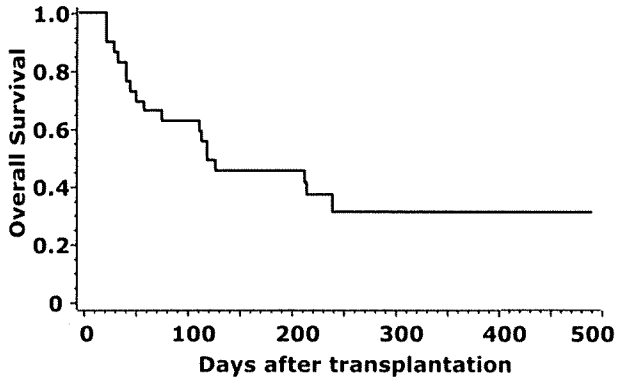

Fig. 6 Probability of overall survival after reduced-intensity unrelated cord-blood transplantation. Estimated 1-year overall survival was 32.7% (95% confidence interval, 14.3–51.1%).

al. (23) reported neutrophil recovery in 90% of patients by a median of 27 days after UCBT, which was significantly delayed compared with allo-HSCT. The delay has been attributed to the limited cell dose in the reports on myeloablative UCBT. The median nucleated cell dose in our study (3.1×10^7/kg) was greater than those in some reports from Western countries (2.1×10^7/kg; Ref. 9). The low median body weight (52 kg) in the Japanese population may favor neutrophil engraftment, whereas our results showed no association between the cell dose and engraftment in the small sample size. In the present study, median time to engraftment was 17.5 days (range, 10–54 days), which was much faster than that reported in previous studies on myeloablative UCBT (7–9). Our results were comparable with the report on adult RI-UCBT by Barker *et al.* (21). Their results showed neutrophil engraftment on a median of 26 days after busulfan/fludarabine/TBI 2 Gy and 9.5 days after cyclophosphamide/fludarabine/TBI 2 Gy. Whereas the reason for the difference remains unclear, these findings suggest that fludarabine-based reduced-intensity regimens enable rapid and stable engraftment.

TRM within 100 days was 27% in this study, which is lower than those reported on myeloablative UCBT (Refs. 7, 9, 24; 32–51% in pediatric patients and 56–63% in adults). Given the relatively old age (median, 58.5 years) and advanced stages of the primary diseases, our reduced-intensity preparative regimen probably decreased TRM. Our TRM within 100 days is comparable with that of 28% in adult RI-UCBT by Barker *et al* (21).

All of the patients tolerated our preparative regimen without grade IV RRT (Bearman's criteria; Ref. 2). Four patients developed grade III RRT with common involvements of the gut, kidney, and liver (Table 3). We used melphalan, which has dose-limiting toxicities of the gut and liver (25). These remained mild without hepatic veno-occlusive disease. Because renal toxicities of fludarabine, busulfan, and TBI 4 Gy are reportedly minimal, the high incidence of renal toxicity might be attributable to concomitant administration of nephrotoxic agents such as cyclosporin and antibiotics. Elderly patients might be susceptible to RRT. We plan to investigate optimal dosages of cyclosporin in RIST for elderly patients. Because TBI, even at a low dose, sometimes causes significant late toxicities in the lung (22), long-term follow-up is required.

Little information on GVHD after RI-UCBT is available. In the present study, the incidences of grade II-IV and III-IV acute GVHD and chronic GVHD were 27%, 23%, and 23%, respectively, whereas some reported those to be 33–44%, 11–22%, and 0–25%, respectively, in myeloablative UCBT (7, 8, 26). There are no significant differences in the incidences of GVHD between myeloablative UCBT and RI-UCBT. This is similar to the GVHD incidences in myeloablative allo-HSCT and RIST (27). Median onset of acute GVHD was 36 days (range, 17–66 days) in the present study, which was comparable with that of myeloablative UCBT (7, 8, 26). In contrast, the achievement of complete donor chimerism and the onset of acute GVHD are delayed in RIST compared with myeloablative allo-HSCT (27, 28). CB might have a potential of intense graft-*versus*-host effect, allowing niche for early engraftment. The characteristics of GVHD after RI-UCBT remain to be investigated, including different organ involvements and response to immunosuppressive treatment.

Interestingly, 20 patients developed inflammatory reactions before engraftment (Table 4). These reactions included noninfectious high-grade fever, eruption, diarrhea, and jaundice, starting on a median of day 9. Because the reactions preceded engraftment (median, day 17.5), we speculated that some form of immune reaction that is not categorized as acute GVHD occurs after RI-UCBT without achieving engraftment. The pre-engraftment fever has been reported on rare occasions in previous reports of UCBT and might be similar to those observed after haploidentical transplantations. Antithymocyte globulin and corticosteroids, which have strong immunosuppressive properties, were commonly used in previous studies on UCBT (9), whereas neither was used in the present study. Immunosuppressive treatment with corticosteroids was effective for the pre-engraftment fever. These findings support that immune-mediated reactions after UCBT might manifest easily with the present regimen. The doubling time of cultured CB $CD34^+$ cells is 7–10 days, which is several hundred-fold faster than that of cultured adult marrow cells (29). Mononuclear cells from CB display a unique cytokine profile such as comparable levels of

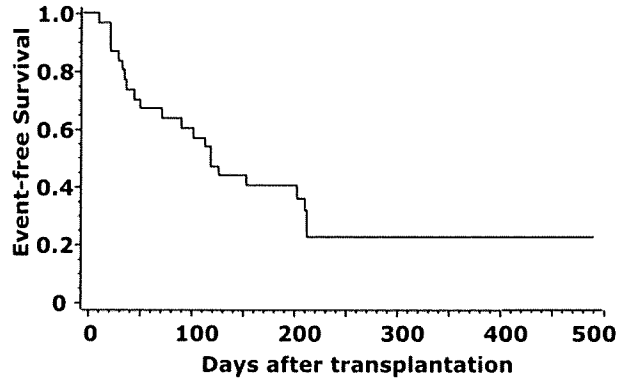

Fig. 7 Probability of event-free survival after reduced-intensity unrelated cord-blood transplantation. Estimated 1-year event-free survival was 22.2% (95% confidence interval, 5.9–38.5%).

interleukin (IL) 2, IL-6, and tumor necrosis factor α, reduced levels of IFN-γ and IL-10, and complete absence of IL-4 and IL-5 (30, 31). Pre-engraftment fever is possibly attributable to a cytokine storm induced by massive proliferation of cells with a unique cytokine profile. Another possibility is homeostasis-driven proliferation of naive T cells in highly immunosuppressed individuals, as demonstrated in murine models (32, 33). This reaction is reportedly associated with cytotoxic cytokines (32, 33). Fever as a transient response to contamination with maternal blood or cells during CB collection cannot be excluded (34). Reactivation of human herpesvirus 6 might be associated with this complication (35). If pre-engraftment fever exerts some antitumor effects, it is reasonable that patients with advanced and chemorefractory hematological diseases achieved long-term remission after RI-UCBT in the present study.

Infection is a common and significant problem in myeloablative UCBT (8, 9, 24), but little is known in RI-UCBT. The present study demonstrated that infection is also problematic in RI-UCBT. Twelve patients developed infection in this study, 9 of whom had been on corticosteroid therapy. Eight of 11 patients with CMV antigenemia had received corticosteroids. Delayed immunological reconstitution with or without GVHD, pre-engraftment fever, and corticosteroids may be risk factors for infection. Appropriate management of GVHD and pre-engraftment fever warrants additional investigation.

One-year OS was 35% in the present study, showing that some patients with advanced hematological malignancies can achieve durable remission after RI-UCBT. Contrary to our prediction, primary diseases recurred only in 3 patients. The candidates for RI-UCBT have extremely poor prognosis with conventional salvage chemotherapy. These findings suggest that RI-UCBT exerts strong antitumor activity and is promising for patients with refractory hematological malignancies without an HLA-identical sibling or an unrelated donor. In contrast, it is premature to apply RI-UCBT to low-risk diseases.

In conclusion, our study demonstrated the feasibility of RI-UCBT for adult patients with advanced hematological diseases, although the limitations included the small sample size and short follow-up. If CB is feasible for adults as an alternative stem cell source, RI-UCBT may become the choice of treatment for patients with advanced hematological diseases that are incurable with conventional treatments. RI-UCBT is particularly appealing for patients who require urgent treatments. Although RI-UCBT is currently associated with a high TRM, this study provided a rationale for continuing our clinical trials. Additional investigations need to focus on minimizing adverse effects including RRT, GVHD, and pre-engraftment immune reactions, whereas preserving graft-*versus*-leukemia effects.

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Bone Marrow Transplantation (2005) 36, 205–213

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Allografting

Reduced-intensity hematopoietic stem-cell transplantation for malignant lymphoma: a retrospective survey of 112 adult patients in Japan

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Summary:

We conducted a nation-wide survey of 112 adult Japanese patients who underwent reduced-intensity stem cell transplantation (RIST) from 1999 to 2002. Underlying diseases included indolent ($n=45$), aggressive ($n=58$) and highly aggressive lymphomas ($n=9$). Median age of the patients was 49 years. A total of 40 patients (36%) had relapsed diseases after autologous stem cell transplantation and 36 patients (32%) had received radiotherapy. RIST regimens were fludarabine-based ($n=95$), low-dose total body irradiation-based ($n=6$) and others ($n=11$). Cumulative incidences of grade II–IV acute graft-versus-host disease (GVHD) and chronic GVHD were, respectively, 49 and 59%. Cumulative incidences of progression and progression-free mortality were 18 and 25%, respectively. With a median follow-up of 23.9 months, 3-year overall survival rates were 59%. A multivariate analysis identified three significant factors for progression, which are history of radiation (relative risk (RR) 3.45, confidential interval (CI) 1.12–10.0, $P=0.03$), central nervous system involvement (RR 6.25, CI 2.08–20.0, $P=0.001$) and development of GVHD (RR 0.28, CI 0.090–0.86, $P=0.026$). RIST may have decreased the rate of transplant-related mortality, and GVHD may have induced a graft-versus-lymphoma effect. However, whether or not these potential benefits can be directly translated into improved patient survival should be evaluated in further studies.
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Allogeneic stem cell transplantation (allo-SCT) is a curative treatment for advanced malignant lymphoma.[1,2] Initially, the benefit of allo-SCT was thought to be largely dependent on the intensity of the conditioning regimen prior to transplantation. Recently, an additional benefit of allo-SCT is derived from an allogeneic graft-versus-malignancy (GVM) effect that reduces the likelihood of disease relapse following transplantation.[3–6] With high regimen-related toxicity (RRT) and treatment-related mortality (TRM), high-intensity, myeloablative conditioning regimens are being replaced by reduced-intensity or nonmyeloablative conditioning regimens. The preliminary data suggest improved survival rates due to decreased TRM.[7] Reduced-intensity stem cell transplantation (RIST) is potentially a curative treatment for heavily pretreated, elderly patients; however, little information is available regarding the outcomes of RIST for malignant lymphoma. We retrospectively analyzed the outcome of RIST. The purpose of this study was to elucidate the treatment-related toxicity of RIST and to evaluate the impact of a potential graft-versus-lymphoma (GVL) effect.

Patients and methods

Data collection

We conducted a nation-wide retrospective survey of 112 adult Japanese patients who underwent RIST from 1999 to 2002 in 32 participating hospitals. All of the RIST recipients who were eligible in this study were included in each hospital. In Japan, approximately 2000 transplants are performed annually. The types of transplantation are autologous (40%), myeloablative allogeneic (45%), and

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