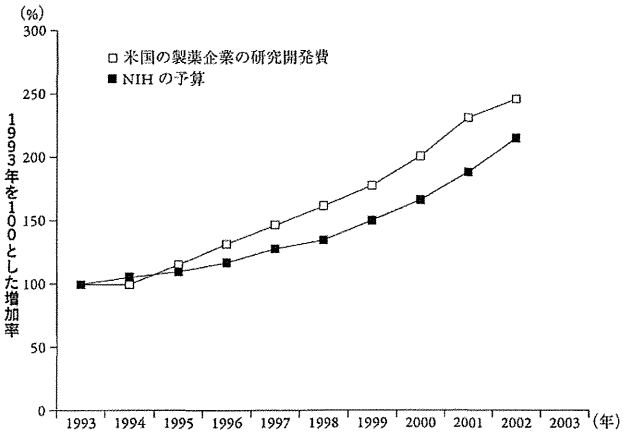

図1　米国における製薬企業の開発費とNIH予算の増加状況
出所：FDA：Challenge and Opportunity on the Critical Path to New Medical Products. 2004

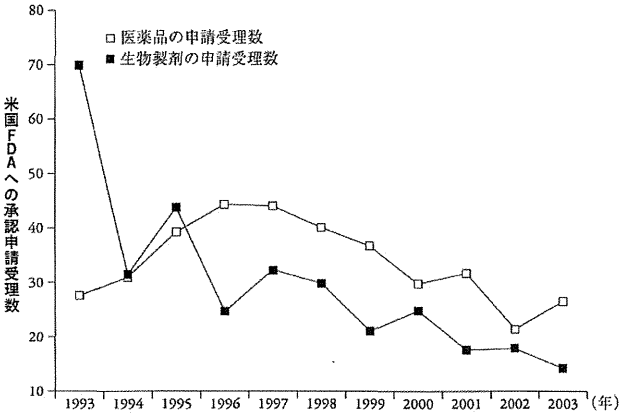

図2　米国FDAでの医薬品・生物製剤の承認申請受理数
出所：FDA：Challenge and Opportunity on the Critical Path to New Medical Products. 2004

競争の大きな柱に成長している．本稿では，このように大きな役割を果たすようになったTRの意義と今後の課題について述べる．

基礎研究と臨床をつなぐトランスレーショナルリサーチの意義

TRは，欧米では“From bench to bedside”とも呼ばれ，日本でも基礎研究と臨床をつなぐ「橋渡し研究」とも呼ばれる．従来の医薬品開発では，有効性分を含んでいそうな材料の探索，そこからの化合物の収集，そして新規化合物の薬効を見極めるスクリーニングを経て候補物を選択することが主流であった．一方，近年ではヒトゲノム解析計画により人間の設計図とも呼べる全ゲノム配列が明らかとなり，また，疾患の発症機序や病態の特徴に関与するメカニズムが分子生物学的に急速に明らかとなってきている．このような知見を基にして治療手段を考案し，臨床開発を進めるのがTRである．そのため，開発のアプローチは抗体に留まらず，核酸医薬，再生・細胞療法，遺伝子治療等多岐にわたる．また，化合物の選択も，鍵となる重要な分子に作用する候補分子としてスクリーニングを行ったり，立体構造と親和性から候補物質のスクリーニングを行ったりするなど変化している．

表1　医薬品世界売り上げランキング

	2002年			2012年		
順位	商品名	薬効	売上	商品名	薬効	売上
1	リピトール	高脂血症薬	8,507	ヒュミラ	TNFα抗体	9,603
2	エポジェン／プロクリット／エスポー	エリスロポエチン	6,675	レミケード	TNFα抗体	9,071
3	ゾコール／リポバス	高脂血症薬	5,580	エンブレル	TNF受容体	8,476
4	タケプロン／プレバシッド	抗潰瘍薬	4,695	アドエア／セレタイド	吸入喘息薬	8,216
5	プリロセック／オメプラール	抗潰瘍薬	4,687	クレストール	高脂血症薬	7,430
6	ノルバスク／アムロジン	降圧薬/Ca拮抗薬	4,174	リツキサン	抗CD20抗体	7,227
7	メバロチン／プラバコール	高脂血症薬	3,755	ランタス	インスリン製剤	6,555
8	ジプレキサ	統合失調症薬	3,689	ハーセプチン	抗HER2抗体	6,444
9	パキシル／セロクサット	抗うつ薬（SSRI）	3,297	アバスチン	抗VEGF抗体	6,307
10	セレブレックス	抗炎症薬（Cox2阻害）	3,150	ジャヌビア	糖尿病薬	6,208

売上は単位百万ドル．　は分子標的薬を示す．
出所：セジデム・ストラテジックデータ（株）ユート・ブレーン事業部

1. 基礎研究を担うアカデミア

TRの基となる基礎研究の主体は，実際には大学等のアカデミアである．製薬企業側からも「産業側は自社シーズ主体に創薬研究を行い製品を作り出すといういわゆる『自前主義』のビジネスモデルは既に断念し，オープンイノベーションの旗印の

表2　米国FDAで承認された医薬品の発明元（1998年から2007年）

	製薬企業	バイオベンチャー	アカデミア
全医薬品（252品目）	58%	18%	24%
優先審査＊（123品目）	46%	23%	30%
科学的新規性の高い医薬品（118品目）	44%	25%	31%

＊priority review：既存の治療に対して大きな優越性を示す場合か，十分な治療法のない疾患あるいは進行度に対する薬剤が指定される．通常は10か月以内の審査期間が6か月以内に短縮される．
出所：文献2）より

下，アカデミアを含め広く外部に創薬シーズを求めるべく産学連携を進めている」とされている[1]．1998年から2007年に米国FDAで承認申請が受理された医薬品252品目の開発元を特許の帰属先から解析した研究では，**表2**に示すように申請が受理された医薬品，優先審査に指定された医薬品，科学的に新規性が高い医薬品で分類してみると，ベンチャー企業発医薬品では18%，23%，25%，アカデミア発では24%，30%，31%であり，医療上必要性あるいは科学的新規性の高い医薬品でベンチャー企業発とアカデミア発が増えている[2]．ただし，ベンチャー企業発の医薬品の元々の開発主体はアカデミアであったことが多く，実際にはアカデミアの研究に基づく医薬品がこの数値よりも多いことが推測される．また，この論文での承認申請は2007年までであり，その後アカデミアでの基礎研究が基となっている医薬品の候補は増えていると推定され，アカデミアの基礎研究が医薬品開発の大きな柱と言える．また，**表1**の分子標的薬6剤のうち，5剤がベンチャー企業で開発され，大手製薬企業に特許権が譲渡されたか，あるいはベンチャー企業が買収されて市販化されたという事実もある．また，収益の面からも，分子標的薬，特に抗体は薬価が非常に高いこともあり，**表1**に示されるように売上額も高くなり製薬企業にとっては大きな収益の柱となっている．

このように，医薬品開発は従来型が低分子化合物を中心とし患者数が多い疾患を対象とした自社開発から，アカデミアが開発主体でアンメット・メディカル・ニーズを対象としたTRに移ってきている．それゆえ，市場規模も大きく何より健康に直結した医薬品開発の国際競争においてTRの促進は国家的課題となってきている．

2. 臨床からの橋渡し事例

一方，新たな医薬品開発だけではなく，ある医薬品の有効性および副作用について個人差が生じる原因の追究は長年の課題であった．これについては，多くの臨床情報，すなわち患者のゲノム情報あるいは悪性腫瘍であれば腫瘍細胞の遺伝子変異を基にした研究が精力的に行われてきた．

患者側の遺伝子多型の差が臨床に用いられている代表例としては，抗がん剤のイリノテカンではUGT1A1の遺伝子多型が代謝に影響し副作用に関連していること[3]，C型肝炎ウイルス感染者でのペグインターフェロンとリバビリンの併用療法でインターフェロンの関連遺伝子であるIL28B遺伝子のSNP（遺伝子多型）が有効性に関連していることが判明し，前者は保険適用となり添付文書にも記載され，後者は先進医療として認められている[4]．腫瘍細胞の例としては，セツキシマブでは血管新生に関連するEGFR陽性が適応であるが，KRASに変異が存在すると有効性を認めないことが明らかとなっている[5]．

このような研究には多くの患者の情報を基に，ゲノム解析というバイオロジー，すなわち基礎研究に立ち返って初めてなされることができる．このような研究を特にがんの領域ではTRに含めたり，あるいは「バックTR」「リバースTR」と呼ばれることもある．単に基礎から臨床への一方通行ではなく，パーソナライズド・メディシン（個別医療）実現のための双方向性と捉えられており治験段階からの検討と合わせ積極的に推進されている．

トランスレーショナルリサーチの状況と課題

1. 知的財産の扱い

日本で産学の連携が促進されるようになったのは1990年代後半に入ってからである．そのため，特許権確保の意識が研究者の間では希薄であった．このような産業界との連携が不十分であったこと，あるいは特許権を取得しなかったことから，日本のアカデミアで発見したことが日本国内ではなく海外企業によって医薬品開発に結びついた例は多い．

最近では特許出願後に論文発表で公表することが一般的になりつつあるが，研究者に対する知財に関する教育機会の不足もあり十分に浸透しているとは言い難い．また，関連特

許まで取得する「強い特許」となるための特許戦略や出願における権利範囲は科学的論理とは異なるため弁理士の能力に依存するが，バイオに精通した弁理士はまだ少ない．アカデミアにおいて特許を管理する部署も十分に機能していないケースもあるため，製薬企業からすると開発には不十分であると判断されるケースも多い．

最近，ALK融合遺伝子を有する非小細胞性肺がんに対するクリゾチニブは，その有効性とともに標的分子の論文発表から承認まで約4年という開発期間の短さが注目を集めた．これは論文に注目した海外企業が早期に治験を開始し承認に至った例である．一方，国内での産学間での連携強化と迅速な開発が，海外との開発競争において未だ十分ではない警鐘ともいえる．

2. 開発にかかるコストと人材不足

先に述べたように，TRの特徴の1つは低分子化合物だけではなく，多くの新しい概念の治療方法が存在することである．企業側からすると新たな製造設備の建設等のコスト，非臨床試験ならびに臨床試験での評価方法・実施方法等未知の領域が多いという理由から，開発に躊躇する場合が多い．また，前述したように特許権が不十分であり他者との競合に耐えられそうにないと判断されることがある．そのため，開発に関心を示す企業が現れないことが多い．その場合，開発するに十分な知財権があれば，医師主導治験を含む臨床試験を研究者が実施し，有効性・安全性に関するデータを取得して再度企業にアプローチすることができる．

このように自ら開発を主体的に行う場合には，**表3**にまとめた，シーズ（研究開発する対象）としての初期の臨床試験の段階までにわたって多くの事項を行う必要がある．これは製薬企業の果たしている資金確保，各種専門家の確保，プロジェクトマネジメントを含む開発戦略の策定等の役割を研究者が行う必要があることを意味する．被験物確保の点からは，近年，再生医療あるいは免疫担当細胞を用いたがん免疫療法開発が盛んであるが，多くの場合，患者由来細胞を原料としており，ヒトに投与することのできる品質を確保できる細胞調製施設（Cell Processing Center；CPCあるいはCell Processing Facility；CPF）をアカデミアで保有・運営する必要がある．このような施設は建設，維持に多額の費用が必要であり，ヒトに投与するに足る品質を有する被験物の製造と管理をアカデミアが担う必要があることもTRの実施が困難であった一因であった．生物統計家，データ解析，プロジェクトマネジメント等の専門家の不足は海外と比して著しく，養成が急務となっている．

表3　開発型トランスレーショナルリサーチで考慮する事項

基礎研究段階
• 動物実験を含めた研究倫理
• 知的財産確保と強化
• 研究資金の確保
非臨床試験段階
• 治験申請に必要な非臨床試験のデザインと実施
• Good Laboratory Practice（医薬品の安全性に関する非臨床試験の実施基準）遵守が必要な非臨床試験の選定と委託
• 適切な動物実験施設
• 被験物製造（細胞調製施設等）
• 規制対応
臨床試験段階
• 製造設備の維持・管理（細胞調製施設等）
• Good Manufacturing Practice（医薬品及び医薬部外品の製造管理及び品質管理の基準）準拠被験物の委託製造あるいは製造
• 特殊検査の対応
• 標準業務手順書の作成・文書管理
• 実施計画書・説明同意文書等の作成
• データマネジメント
• モニタリング・監査等の質の保証業務
• 補償・賠償への対応
• 規制対応
全段階を通じて
• 研究，非臨床試験，臨床試験実施に必要な費用の確保
• 利益相反管理
• 連携・導出企業の選定
• プロジェクトマネジメント

「日本版NIH構想」への期待

このような開発環境を研究者個人で整えるのは困難であり，日本のアカデミアとしても組織として整える必要があった．そこで，文部科学省では，TRの支援の拠点形成のために平成19（2007）年度に橋渡し研究支援プログラムを開始し，次いで平成24（2012）年度からの橋渡し研究加速ネットワークプログラムでは開始時に全国で7拠点を選定している[6]．このプログラムでは，拠点外のアカデミアも含めたシーズの知財獲得から医師主導治験の実施までを支援することのできる支援体制を構築するために，専門的に業務を遂行できる人材の養成・確保，教育体制の整備，細胞調製施設を含めた施設整備等が求められている．このプログラムにより拠点整備は進行しているが，いわゆる「日本版NIH構想」において，厚生労働省の早期・探索的臨床試験拠点整備事業および臨床研究中核病院整備事業が平成27（2015）年度に一体運用される計画となっており，省庁の垣根を越えた支援が期待されている．また，橋渡

し研究加速ネットワークプログラムの予算は，平成25（2013）年度が約30億円で平成26（2014）年度は約65億円と異例ともいえる増額となっており国の期待もうかがうことができる．

米国ではNIHは世界最大の基礎研究所というだけでなく，研究所病院を有するTR開発施設であり，また，研究費の配分あるいは医療開発の実務支援を一元的に行う国策としての医薬品開発の事実上の司令塔となっている．NIHが臨床研究に費やす予算は年間約300億ドルであり，約80％が競争的資金として分配され，約10％がNIHの施設に分配されている[7]．NIHのアカデミアのTR拠点への支援としては，National Center for Advancing Translational Sciencesを創設し，Clinical and Translational Science Awards（CTSA）を設けていることが挙げられる．CTSAでは米国の62の施設が拠点として選定され，総額4.6億ドルが各センターに配分され，各センターには年間約400万ドルから約2,300万ドルが支出されている[8]．その他，NIHは，低分子化合物や抗体の治験用製造施設を関連企業として有しており，また，他のアカデミア向けに細胞調製を行う拠点の指定による治験での被験物提供体制を整えており，TRの問題の1つである被験物の確保を容易にしている．また，NIH発のシーズの開発やライセンスアウト，NIHから研究費を配分された試験の実施に必要な資料整備等の支援を行っており，治験実施施設支援の役割も果たしている．

日本においても急速にTR推進のための環境が整備されつつある．しかし米国と比するとその規模と体制においてまだ格段の差が存在する．医薬品開発の大きな柱であるTRを国際競争力のあるものにするためには「日本版NIH構想」のもと戦略的かつ継続的な支援が必要である．

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Acute kidney injury after myeloablative cord blood transplantation in adults: the efficacy of strict monitoring of vancomycin serum trough concentrations

H. Mae, J. Ooi, S. Takahashi, S. Kato, T. Kawakita, Y. Ebihara, K. Tsuji, F. Nagamura, H. Echizen, A. Tojo. Acute kidney injury after myeloablative cord blood transplantation in adults: the efficacy of strict monitoring of vancomycin serum trough concentrations. Transpl Infect Dis 2013: **15**: 181–186. All rights reserved

Abstract: *Background.* Acute kidney injury (AKI) is a common medical complication after myeloablative allogeneic stem cell transplantation (SCT). We have previously performed a retrospective analysis of AKI after cord blood transplantation (CBT) in adults, and found that the maximum of vancomycin (VCM) trough levels were significantly higher in patients with AKI. Following these results, we have monitored VCM serum trough concentrations more strictly, to not exceed 10.0 mg/L, since 2008.
Methods. In this report, we performed an analysis of AKI in a new group of 38 adult patients with hematological malignancies treated with unrelated CBT after myeloablative conditioning between January 2008 and July 2011.
Results. Cumulative incidence of AKI at day 100 after CBT was 34% (95% confidence interval 19–50). The median of the maximum value of VCM trough was 8.8 (4.5–12.2) mg/L. In multivariate analysis, no factor was associated with the incidence of AKI. No transplant-related mortality was observed. The probability of disease-free survival at 2 years was 83%.
Conclusion. These findings suggest that strict monitoring of VCM serum trough concentrations has a beneficial effect on outcomes of CBT.

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Key words: vancomycin; myeloablative conditioning; cord blood transplantation; acute kidney injury

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Acute kidney injury (AKI) is a common medical complication early after myeloablative allogeneic stem cell transplantation (SCT). The incidence of AKI, defined as a 2-fold rise in serum creatinine (sCr) concentration from baseline, has been reported ranging from 36% to 72% in SCT in a myeloablative setting (1–7), and about 20% required hemodialysis. We have previously reported a retrospective analysis of AKI in a group of 54 adult patients with hematological malignancies who received unrelated cord blood transplantation (CBT) after myeloablative conditioning between 2004 and 2007 (8). A statistically significant decrement of renal function from baseline was observed between days 11 and 20. Among the 54 patients, AKI occurred in 27.8% and was associated with a high mortality rate. Although no difference was seen in maximum cyclosporine (CYA) trough levels, the maximum vancomycin (VCM) trough levels were significantly higher in patients with AKI (8). Following these results, we have monitored VCM serum trough concentrations more strictly. In this report, we performed an analysis of AKI in a new group of 38 adult patients with hematological malignancies treated with unrelated CBT after myeloablative conditioning between January 2008 and

July 2011. The main purpose of this retrospective single-center study was to confirm the efficacy of strict monitoring of VCM serum trough concentrations, as well as to identify factors related to the incidence of AKI.

Patients and methods

Patients

This was a retrospective single-center analysis. Between January 2008 and July 2011, 39 consecutive adult patients with hematological malignancies were treated with unrelated CBT at The Institute of Medical Science, University of Tokyo. We excluded 1 patient who experienced primary engraftment failure. A total of 38 patients were analyzed. Patients qualified as standard risk if they were in first or second complete remission, had chronic-phase chronic myelogenous leukemia or refractory anemia of myelodysplastic syndrome, or had no high-risk cytogenetics. Patients in third complete remission, in relapse, or in refractory disease, with chronic myelogenous leukemia beyond chronic phase, or with high-risk cytogenetics were classified as high risk. Analyses of data were performed in December 2011. Written informed consent for treatment was obtained from all patients.

Conditioning

All patients received 4 fractionated 12 Gy total body irradiation on days −8 and −7, in addition to cytosine arabinoside (Ara-C) and cyclophosphamide. Ara-C was administered intravenously (IV) over 2 h at a dose of 3 g/m^2 every 12 h on day −5 and −4 (total dose 12 g/m^2). In patients with myeloid malignancies, recombinant human granulocyte colony-stimulating factor (G-CSF) was combined with Ara-C. G-CSF was administered by continuous infusion at a dose of 5 μg/kg/day. Infusion of G-CSF was started 12 h before the first dose of Ara-C and stopped at the completion of the last dose. Cyclophosphamide was administered IV over 2 h at a dose of 60 mg/kg once daily on days −3 and −2 (total dose 120 mg/kg). Two days after the completion of conditioning, patients received a CBT.

Graft-versus-host disease (GVHD) prophylaxis

All patients received standard CYA and methotrexate as GVHD prophylaxis. CYA was given IV every day starting on day −1 at a dose of 3 mg/kg/day. Methotrexate (15 mg/m^2 IV) was given on day 1, and 10 mg/m^2 on day 3 and 6. Once oral intake could be tolerated, patients were administered oral CYA at a dose of 1:2, in 2 divided doses per day, based on the last intravenous dose. CYA was reduced when sCr levels rose above 1.5 times baseline, or other serious agent-associated toxicities occurred. Physicians could freely modify the CYA dose for patients experiencing severe acute GVHD (aGVHD) or risk of disease relapse. Corticosteroid-based treatment was considered when grade II or higher severe aGVHD occurred (0.5–2 mg/kg).

Supportive care

All patients received G-CSF by intravenous infusion starting on day 1 until durable granulocyte recovery was achieved. The supportive care regimen, including prophylaxis for infection was the same as previously reported (8, 9).

Monitoring

All patients were monitored retrospectively 10 days before, and after the first 100 days, of CBT. Daily laboratory data collecting and the detecting method of VCM and CYA trough concentration were the same as previously reported (8). Therapeutic drug monitoring for VCM by assessing serum trough concentration was done twice in weekly, and modified to not exceed 10.0 mg/L.

End-points and definitions

AKI was defined as 2-fold rise in sCr concentration on daily laboratory results from the baseline (the average of days −10 to 0). Myeloid engraftment was defined as the first of 3 consecutive days, during which the absolute neutrophil count was at least 0.5×10^9/L. Platelet recovery time was achieved on the first of 3 days when the platelet count was higher than 50×10^9/L without transfusion support. The aGVHD was graded according to previously published criteria (10). Transplant-related mortality was defined as death from any cause except relapse. Relapse was defined by morphologic evidence of disease in peripheral blood, bone marrow, or extramedullary sites. Disease-free survival was defined as the time from CBT to relapse, death, or the last observation.

Statistical analysis

Continuous variables are expressed as median and their range. For dichotomous variables, the frequencies of positive occurrence are given along with their corresponding percentages. Continuous variables were divided into high or low with their median values, and a single VCM trough concentration of 10.0 mg/L was defined as a threshold level for analysis. Cumulative incidence of AKI was estimated with competing risk setting, of which death and relapse were defined as competing risk events. Variables considered in univariate analysis were body weight, age, recipient gender, recipient cytomegalovirus serology, disease status at transplant (standard or high risk), total nucleated cell dose, CD34+ cell dose, baseline sCr levels, VCM use, VCM trough levels, CYA trough levels, foscarnet use, aminoglycosides use, days of neutrophil engraftment, aGVHD grade 3–4, and positive blood culture result. Variables with a *P*-value <0.1 for cumulative incidence of AKI were tested in multivariate analysis using Cox proportional hazards models, and *P*-values <0.05 were considered to be statistically significant. The probability of disease-free survival was estimated from the time of CBT according to the Kaplan–Meier method. Endpoints were calculated at the last contact, the date of the last follow-up being December 1, 2011. Statistical software R, version 2.12.2, was used for analysis.

Results

Characteristics of patients and cord blood units

The characteristics of 38 patients and cord blood units are shown in Table 1. Among the patients, the median age was 41.5 years (range, 18–52 years), the median weight was 59.5 kg (range, 39–76 kg), the median number of cryopreserved nucleated cells was 2.8×10^7/kg (range, 1.7–5.7 $\times$ 10^7/kg), and the median number of cryopreserved CD34+ cells was 0.9×10^5/kg (range, 0.4–2.6 $\times$ 10^5/kg). All patients received a single and human leukocyte antigen-mismatched cord blood unit.

Time courses of changing renal function

No patient had confirmed renal dysfunction before transplantation. The changes of renal function as variations (%) of sCr from baseline levels observed on days 11–20 were greatest and significant (+15.8%,

Characteristics and clinical course

Characteristics	
Patients, *n*	38
Male/Female, *n*	25/13
Median age, years (range)	41.5 (18–52)
Median weight, kg (range)	59.5 (39–76)
Median number of cryopreserved nucleated cells, $\times 10^7$/kg (range)	2.8 (1.7–5.7)
Median number of cryopreserved CD34+ cells, $\times 10^5$/kg (range)	0.9 (0.4–2.6)
Recipient CMV status, Positive/Negative, *n*	32/6
Diagnosis	
AML, *n*	12
MDS-related secondary AML, *n*	6
RAEB, *n*	3
RA, *n*	2
CML, *n*	3
ALL, *n*	11
NHL, *n*	1
Disease status at transplant	
Standard risk, *n*	10
High risk, *n*	28
Conditioning regimen	
TBI + Ara-C/G-CSF + CY, *n*	26
TBI + Ara-C + CY, *n*	12
GVHD prophylaxis	
CYA + MTX, *n*	38
Baseline sCr, mg/dL (range)	0.62 (0.33–0.87)
Neutrophil >0.5 $\times$ 10^9/L, days (range)	21 (17–30)
Patients with positive blood culture, *n* (%)	6 (16)
Patients taking aminoglycosides, *n* (%)	32 (84)
Patients taking foscarnet, *n* (%)	10 (26)
Patients taking liposomal amphotericin, *n* (%)	16 (42)
Maximum CYA trough value, μg/L (range)	258.5 (40–453)
Patients taking VCM, *n* (%)	32 (84)
Duration of VCM therapy, days (range)	54 (6–100)
Maximum VCM trough value, mg/L (range)	8.8 (5.2–12.2)
Patients with maximum VCM trough value, >10.0 mg/L, *n* (%)	9 (24)
Patient requiring hemodialysis, *n* (%)	0 (0)

CMV, cytomegalovirus; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess blasts; RA, refractory anemia; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; TBI, total body irradiation; Ara-C, cytosine arabinoside; G-CSF, recombinant human granulocyte colony-stimulating factor; CY, cyclophosphamide; GVHD, graft-versus-host disease; CYA, cyclosporine; MTX, methotrexate; sCr, serum creatinine; VCM, vancomycin.

Table 1

0.57 ± 0.18 mg/dL to 0.71 ± 0.24 mg/dL, $P < 0.001$). No obvious recovery occurred of declined renal function, which remained until day 100.

Incidence and risk factors of AKI

Cumulative incidence of AKI at day 100 after CBT was 34% (95% CI 19–50) (Fig. 1). The median of the maximum value of VCM trough was 8.8 (4.5–12.2) mg/L. In univariate analysis, baseline sCr levels and foscarnet use were associated with the incidence of AKI (Table 2). In multivariate analysis, no factor was associated with the incidence of AKI (Table 2).

Transplant outcomes

All patients had myeloid reconstitution, and the median time to >0.5 × 10^9/L absolute neutrophil count was 21 days (range, 17–30 days). A self-sustained platelet count >50 × 10^9/L was achieved in 37 patients at a median time of 45.5 days (range, 34–127 days). In 37 of 38 evaluable patients, aGVHD occurred. The grading of aGVHD was grade I in 7 patients, grade II in 25, grade III in 4, and grade IV in 1. No one experienced hepatic veno-occlusive disease. Six of 38 patients (16%) had positive blood culture; however, no one had confirmed hypotension, indicated with decrease in systolic blood pressure >10 mmHg to <90 mmHg. Of 6 patients with positive blood cultures, 4 patients were not administered VCM. The total number of positive blood cultures was 13 of 998 specimens. Ten of 13 bacterial pathogens from blood cultures were gram-positive cocci (Table 3). Vancomycin-resistant *Enterococci* were detected in 1 patient from blood culture, however, this had been continuously detected from stool specimens since admission. No patients required hemodialysis. Among the 38 patients, no patient died of transplant-related causes (transplant-related mortality 0%). Six patients relapsed. Of these 6 patients, 5 patients died of relapse. A total of 32 of 38 patients are alive and free of disease at between 139 and 1400 days (median: 634 days) after CBT. The probability of disease-free survival at 2 years was 83% and 77% at 3 years (Fig. 2).

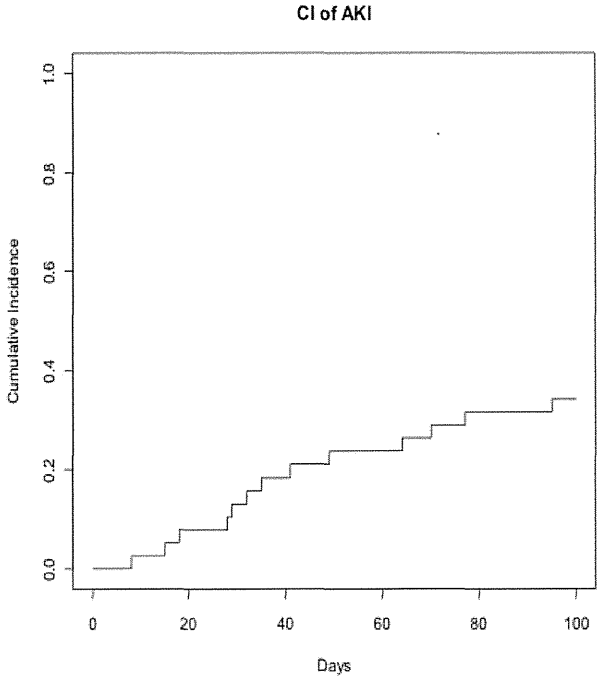

Fig. 1. Cumulative incidence (CI) of acute kidney injury (AKI).

Discussion

In this study, similar trends were observed in the time course of renal function changes as previously reported (8). However, the elevation in sCr was lower in this study, especially in days 11–20 (from 35.0% [8] to 15.8% in this study). Cumulative incidence of AKI was 34%; however, this was not assessed in our previous study (8). When we assessed the incidence of AKI with an identical definition to the previous

Univariate and multivariate analysis of factors associated with acute kidney injury

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Baseline sCr, mg/dL				
>0.62	0.27 (0.08–0.98)	0.047	0.33 (0.08–1.32)	0.12
<0.62	1		1	
Foscarnet				
(+)	3.11 (1.07–9.05)	0.037	2.45 (0.71–8.42)	0.15
(−)	1		1	
VCM trough, >10.0 mg/L				
(+)	2.68 (0.89–8.09)	0.081	2.64 (0.76–9.19)	0.13
(−)	1		1	

CI, confidence interval; sCr, serum creatinine; VCM, vancomycin.

Table 2

Isolated bacterial pathogens from blood cultures

Pathogens	*n*
Enterococcus faecalis	3
Vancomycin-resistant *Enterococcus faecium*	3
Methicillin-resistant *Staphylococcus* species	1
Methicillin-resistant *Staphylococcus epidermidis*	3
Stenotrophomonas maltophilia	1
Bacillus species	1
Bacillus cereus	1

Table 3

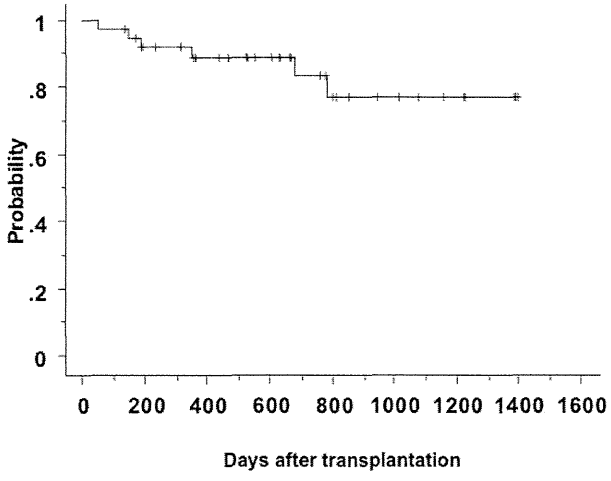

Fig. 2. Probability of disease-free survival after cord blood transplantation.

study, defined as just a 2-fold rise in sCr of 10 days average before and after transplantation, the incidence of AKI decreased to 11% in this study. In our previous study, the maximum VCM trough levels were significantly higher in patients with AKI (8); therefore, we have monitored VCM serum trough concentrations more strictly to not exceed 10.0 mg/L since 2008 in this study period. The average maximum value of VCM trough levels was lowered to 8.7 ± 2.1 mg/L from 12.2 ± 4.6 mg/L in the previous study, and proportion of patients with trough levels >10.0 mg/L was also decreased from 57% to 24%. Although baseline sCr levels and foscarnet use were associated with the incidence of AKI, VCM trough levels were not associated with AKI in univariate analysis. No factor was associated with AKI in multivariate analysis. Parikh et al. (11) reported AKI significantly affects survival after myeloablative allogeneic SCT in their meta-analysis, and more recently, Kagoya et al. (7) as well as Gooley et al. (12) reported the association of severity of AKI classification and non-relapse mortality within 100 days after transplantation. Although cumulative incidence of AKI was 34% in this study, no patients required hemodialysis or died of transplant-related causes. Recently, Yazaki et al. (13) reported the association of overall mortality and early bacterial infection of CBT in adults. They reported that cumulative incidence of early bacterial infection at day 100 was 21%, early bacterial infection had a negative effect on survival for adults, and the median day of development was 10 days after transplant, suggesting that prevention of bacterial infection in the very early post-CBT phase is important. Recently, a shift has occurred in the type of infecting organisms that cause bacteremia from predominantly gram-negative organisms to gram-positive cocci. The same trend is confirmed in the CBT (13, 14). VCM has an important role for infection control of gram-positive bacteremia, and was given to almost all the patients in this study. The reduced susceptibility of staphylococci for VCM has been reported since the mid 1990s, and prolonged exposure to lower VCM concentration has been associated with resistance (15). Although very few studies about pharmacokinetics and pharmacodynamics of VCM are available, several studies revealed area under the curve/minimum inhibitory concentration (AUC/MIC) as a preferred parameter, and AUC/MIC >400 associated with successful outcome and prevention of resistance (15, 16). Because of the difficulty of determining multiple concentrations for calculating AUC in the clinical setting, VCM trough concentrations have been recommended as the best surrogate marker for AUC/MIC, and concentrations of 15–20 mg/L – higher than the 5–15 mg/L previously recommended – is recommended as the target range (16). However, because an increased risk of nephrotoxicity with elevated VCM trough concentrations has been reported, and no appropriate pharmacokinetic/pharmacodynamic parameters for VCM have been determined (15, 17, 18), careful assessments are needed for using VCM at high target concentrations. Although we controlled VCM levels to not exceed 10.0 mg/L in this study, no patient died of bacterial infections. Further studies are required to determine the optimal VCM trough concentrations. Few reports are available about monitoring VCM trough concentrations for preventing AKI in allogeneic SCT in adults. Despite the limitations associated with this retrospective review of a small number of patients, our results suggest that strict monitoring of VCM serum trough concentrations has a beneficial effect on outcomes of CBT.

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Conflict of interest: The authors declare no conflict of interest of this manuscript.

Author contributions: H.M. and J.O. designed the study, analyzed data, and wrote the manuscript; J.O., S.T., S.K., T.K., Y.E., K.T., and A.T. cared for the patients; F.N. performed the statistical analysis; and H.E. and A.T. reviewed the study.

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Unrelated cord blood transplantation after myeloablative conditioning regimen in adolescent and young adult patients with hematologic malignancies: A single institute analysis

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ABSTRACT

We report the results of unrelated cord blood transplantation (CBT) after myeloablative conditioning regimen in 16 patients with hematologic malignancies from 15 to 20 years old. The median times of myeloid and platelet engraftment were 21 and 38 days, respectively. The cumulative incidences of acute graft-*vs*-host disease (GVHD) was 62.0%, all of which were grade I or II, and that of extensive-type chronic GVHD was 12.5%. The probabilities of overall and disease-free survival at 3 years were 68.2% and 48.6%, respectively, comparable to adult or childhood cases. Adolescents and young adult patients with hematologic malignancies who have no HLA-matched adult donors could be considered as candidates for CBT.

1. Introduction

Recently the medical needs of adolescents and young adults with hematologic malignancies have become better defined. In comparison of outcome of patients with 16–21 years of age with acute lymphoblastic leukemia (ALL) treated with pediatric *vs* adult clinical trials, pediatric trials yielded better outcome than adult trials [1]. In patients with acute myelocytic leukemia (AML), outcome of children younger than age 15 years has significantly improved for the last several decades, but that of patients with 15–19 years remains poor [2]. Thus, adolescents and young adults with hematologic malignancies are distinct in terms of their therapeutic requirements compared to adults or children. However, there have been no data defined adolescent and young adult patients for cord blood transplantation (CBT) after conventional myeloablative conditioning regimen. We here first report the clinical results for a group of 16 adolescent and young adult patients with hematologic malignancies treated with CBT in our institute, showing the safety and efficacy comparable to those for adults and children.

2. Patients and methods

This is a retrospective single-center analysis. Between September 1999 and July 2009, 16 patients at adolescent and young adult ages from 15 to 20 years old were treated with CBT as the first allogeneic stem cell transplantation at The Research Hospital, Institute of Medical Science, University of Tokyo. One patient received an autologous bone marrow transplantation before he had come to our hospital. Written informed consent for treatment was obtained from all patients with the Declaration of Helsinki. Patients were qualified as being standard risk and high risk according to the criteria in the previous reports [3,4].

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2.1. HLA typing and donor selection

HLA-A and HLA-B antigens were identified by serological typing. HLA-DRB1 alleles were determined by high-resolution molecular typing using polymerase chain reaction sequence-specific primers. Patients who did not have HLA-matched family or unrelated adult donors were considered to be eligible for CBT. In the selection of cord blood unit for transplantation, all cord blood grafts were evaluated by HLA-A, HLA-B and HLA-DRB1 typing, and nucleated cell counts. Preferred cord blood units matched 4 of 6 to 6 of 6 HLA loci and contained a minimal cell count of 1.5×10^7 nucleated cells/kg body weight before freezing according to the criteria of our institution as shown in the previous reports [3,4]. All cord blood units were obtained from cord blood banks belonging to the Japan Cord Blood Bank Network.

2.2. Conditioning regimen, GVHD prophylaxis, and supportive care

All patients received fractionated 12 Gy total body irradiation and chemotherapy as a myeloablative conditioning regimen (Table 1). Fifteen patients received standard cyclosporin (CsA) and methotrexate (MTX), and one patient received CsA alone for a graft-*vs*-host disease (GVHD) prophylaxis [3,4]. Fifteen mg/m^2 of MTX was given intravenously on day 1, and 10 mg/m^2 on days 3 and 6 as previously reported [3,4]. Both acute and chronic GVHD (aGVHD and cGVHD, respectively) were graded according to the previously published criteria [5,6]. The criterion to stop immunosuppression depended on patients' disease status. All patients received recombinant human granulocyte colony-stimulating factor starting on day 1 until durable granulocyte recovery was achieved.

2.3. Endpoints and statistical analysis

The chimerism status after CBT, engraftment, graft failure, treatment-related mortality (TRM), and disease-free survival (DFS) were defined as described in the previous reports [3,4].

Data analysis was performed on 1 December 2010. The probability of overall survival (OS) and DFS were estimated using the Kaplan–Meier method.

3. Results and discussion

The characteristics of the 16 patients and the cord blood units are shown in Table 1. Six patients were classified as standard risk while 10 patients as high risk. Six patients (2 ALL, 3 myelodysplastic syndrome (MDS) and 1 chronic myelocytic leukemia (CML)) were initially treated by Pediatric units. All patients received a single and HLA-mismatched cord blood unit. The median numbers of cryopreserved nucleated cells and CD34$^+$ cells were 2.50×10^7/kg (range 2.05 to 3.73×10^7/kg) and 0.94×10^5/kg (range 0.46 to 1.33×10^5/kg), respectively. The median numbers of infused nucleated and CD34$^+$ cells were 2.11×10^7/kg ($n = 11$; range 1.36 to 2.38×10^7/kg) and 0.76×10^5/kg ($n = 11$; range 0.25 to 2.55×10^5/kg), respectively.

Fourteen patients (87.5%) successfully achieved myeloid reconstitution and 2 patients went into graft failure regardless of above of median number of total nucleated cells (2.71 and 2.45×10^7/kg, respectively) and CD34$^+$ cells (1.09 and 1.13×10^5/kg, respectively) transplanted. One had full recovery with 100% of host chimerism by day 52, and the other took a second cord blood graft on day 30. All patients with myeloid reconstitution showed full donor chimerism at the first bone marrow examination after CBT. The median time to an absolute neutrophil count >0.5×10^9/L among the patients with engraftment was 21 days (range 19–32 days). The cumulative

Table 1
Characteristics of patients, cord blood units, and outcomes.

Characteristics	
Patients, *n*	16
Male/female, *n*	9/7
Median age, years (range)	17 (15–20)
Median weight (kg) (range)	52 (45–71)
Median number of cryopreserved nucleated cells $\times 10^7$/kg (range)	2.50 (2.05–3.73)
Median number of cryopreserved CD34$^+$ cells $\times 10^5$/kg (range)	0.94 (0.46–1.33)
Median number of infused nucleated cells, *n* $\times 10^7$/kg (range)	11 2.11 (1.36–2.38)
Median number of infused CD34$^+$ cells, *n* $\times 10^5$/kg (range)	11 0.76 (0.25–2.55)
Median time from diagnosis to transplantation Days (range)	429 (65–1898)
Recipient CMV status, positive/negative, *n*	13/3
Diagnosis	
De novo AML [*n* (%)]	3 (19)
CR1, *n*	1
CR2, *n*	1
Not in remission, *n*	1
ALL [*n* (%)]	7 (44)
CR1, *n*	2
CR2, *n*	4
CR3, *n*	1
CML BC [*n* (%)]	1 (6)
MDS [*n* (%)]	4 (25)
RA, *n*	1
RCMD, *n*	1
Advanced (*n*)	2
MDS/MPD [*n* (%)]	1 (6)
Disease status at transplant*	
Standard risk [*n* (%)]	6 (37)
High risk [*n* (%)]	10 (63)
Conditioning regimen	
TBI + CY + AraC, *n*	1
TBI + CY + AraC/G-CSF, *n*	9
TBI + CY, *n*	4
TBI + CY + Tepa, *n*	1
TBI + Flu + Mel, *n*	1
GVHD prophylaxis	
CSP + sMTX, *n*	15
CSP, *n*	1
Number of HLA-A, B, DRB1 mismatches	
1, *n*	4
2, *n*	5
3, *n*	6
4, *n*	1
Engraftment [day (range)]	
Median time to neutrophil count >0.5×10^9/L	21 (19–32)
Median time to platelet count >50×10^9/L	38 (33–98)
Acute GVHD [*n* (%)]	
0	1 (7)
Grade I	6 (43)
Grade II	7 (50)
Grade III	0
Grade IV	0
Chronic GVHD [*n* (%)]	
None	0
Limited	10 (83)
Extensive	2 (17)
Immunosuppressant termination ($n = 7$)	
Median time [day (range)]	267 (83–952)
Cause of death [*n* (%)]	
Relapse	4 (80)
MOF	1 (20)

CMV, cytomegalovirus; AML, acute myelogenous leukemia; CR1, CR2, CR3: first, second, third complete remission, respectively; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; BC, blast crisis; MDS, myelodysplastic syndrome; RA, refractory anemia; RCMD, refractory cytopenia with multilineage dysplasia; Advanced, patients with MDS-related secondary AML; MPD, myeloproliferative disease; TBI, total body irradiation; Ara-C, cytosine arabinoside; G-CSF, granulocyte colony-stimulating factor; CY, cyclophosphamide; Tepa, thiotepa; Flu, fludarabine; Mel, melphalan; CsA, cyclosporine; sMTX, short-term methotrexate; MOF, multiple organ failure.

* Patients qualified as being standard risk or high risk according to the criteria described in previous reports [3,4].

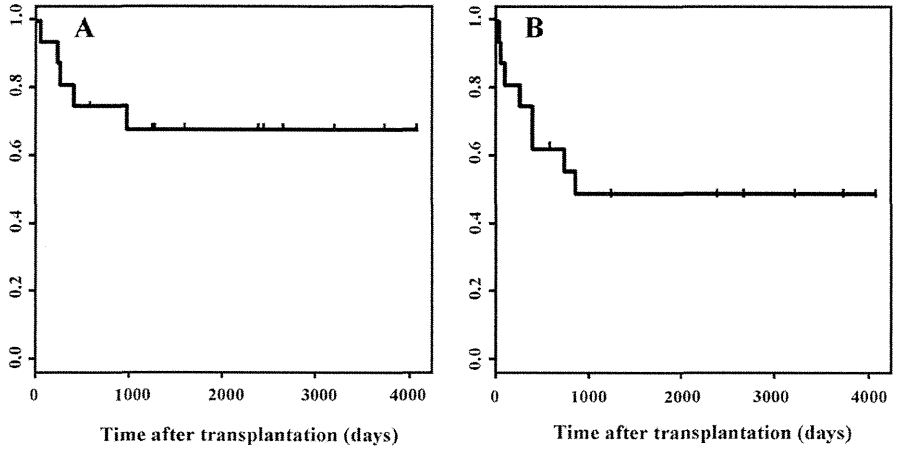

Fig. 1. Kaplan–Meier estimates of overall survival (A) and disease-free survival (B) after cord blood transplantation in adolescent patients with hematologic malignancies. The probability of OS (A) and DFS (B) at 3 years was 67.5% (95% CI, 47.6–95.8%) and 48.6% (95% CI, 29.0–81.4%), respectively.

incidence of neutrophil recovery at day 42 was 87.5% (95% confidence interval (CI), 68.9–100%). A self-sustained platelet count $>50 \times 10^9$/L was achieved in 13 patients at a median time of 38 days (range 33–98 days). The cumulative incidence of platelet recovery at day 100 was 81.3% (95% CI, 57.3–100%). These results using single units showed that the hematopoietic reconstituting ability of unrelated CB in adolescent patients was similar to those in pediatric and adult ones [7–10].

aGVHD occurred in 13 of 14 evaluable patients who survived for more than 100 days, but there were no patients with grades III and IV aGVHD (Table 1). The cumulative incidence of grade I or II aGVHD at day 100 was 62.0% (95% CI, 27.8–96.2%). cGVHD occurred in all of 12 evaluable patients, and 2 among them displayed the extensive type. The cumulative incidence of cGVHD and extensive-type cGVHD at 1 year was 68.8% (95% CI, 43.6–94.0%) and 12.5% (95% CI, 0–29.4%), respectively. There was no relationship between the immunosuppressive therapy and the occurrence of aGVHD and cGVHD. TRM only occurred in one patient. This patient suddenly suffered an infarction in the pons on day 22 after CBT, and died of multiple organ failure (MOF) on day 43. The cumulative incidence of TRM at 1 year was very low (6.3%). Consequently GVHD was not related to TRM in our study. The relatively higher incidence of GVHD in our study may come from earlier discontinuation of immunosuppressant as reported previously [3,4].

However, 2 of 6 standard risk patients and 5 of 10 high risk patients relapsed. The cumulative incidence of relapse at 3 years was 45.1% (95% CI, 18.8–71.4%). All of the relapsed patients received chemotherapy to obtain remission, and five patients received a second CBT. To find the risk factors to relapse after CBT in adolescent and young adult patients, we analyzed the relationships between the relapse and the numbers of infused nucleated and $CD34^+$ cells, GVHD prophylaxis and the number of HLA-mismatches, but there were no significant relationships. In the patients with ALL, 1 out of 2 patients, who were treated by pediatric-type regimen before CBT, and 3 out of 5 patients, who were treated by non-pediatric-type regimen, relapsed. Although it was shown that pediatric-type regimen is favorable for the treatment of adolescent and young adult patients in ALL [1], there was no significant relationship between the relapse after CBT and the treatment with pediatric-type regimen in this study. However, since the number of patients was small in our single institute analysis, further study with a larger number of patients may be needed to find the risk factor to relapse after CBT.

Eight patients are alive and disease-free at the median 97 months (range 20–135 months) after transplantation. The disease-free patients included the patient who underwent autologous bone marrow recovery without relapse. All of the alive patients had a good performance status with 90–100% Karnofsky score at the time of analysis. The probabilities of OS and DFS at 3 years were 67.5% (95% CI, 47.6–95.8%) and 48.6% (95% CI, 29.0–81.4%), respectively (Fig. 1A and B). The probability of DFS at 3 years in the standard risk patients was 66.7% (95% CI, 37.9–100%) while that in the high risk group was 40% (95% CI, 18.7–85.5%). Atsuta et al. reported that OS and DFS at 2 years in adult cases who received CBT were 48% and 42% in AML, and 52% and 46% in ALL, respectively [11]. Eapen et al. also showed that DFS at 2 years was 44% in remission cases and 15% in non-remission cases at CBT in adults [12]. Pediatric studies reported that OS at 2 years was 45.5%[9] and DFS at 5 years was 33–60% [10]. Thus, both DFS and OS in the present study were comparable to those in adult and pediatric patients.

However, in the previous report by our institute, the 3-year probability of DFS after unrelated CBT for hematological malignancies was higher (70%) than that in the present report, especially in the standard risk patients (93% *vs* 67%) [4]. In comparison with the previous report, the overall rate of high risk patients (62% *vs* 57%), the 1-year incidence of TRM (6% *vs* 9%), the 100-day incidence of aGVHD (62% *vs* 52%) and the cumulative incidence of cGVHD in patients surviving more than 100 days (69% *vs* 71%) were almost similar. In contrast, the 3-year cumulative incidence of relapse was significantly higher in the present study (45% *vs* 17%). Therefore, the difference in DFS between the present and previous reports might have been caused by the biological characteristics of hematological malignancies in adolescence, such as the resistance of malignant cells to anti-cancer drugs or immunological immaturity reducing the graft-*vs*-malignant cell effect. Accordingly, further improvement in the pre-transplantation chemotherapy, conditioning regimen and post-transplantation immunomodulation may be needed to achieve better outcomes during the treatment of adolescent hematologic malignancies with unrelated CBT.

In summary, although our patient cohort was small, our results suggested that CBT after myeloablative conditioning regimen could be safe for adolescents and young adult patients with hematologic malignancies as well as pediatric and adult patients. However, since the adolescent hematologic malignancies are thought to be relatively chemoresistant, a therapeutic regimen that takes the biological characteristics of these malignancies into account would contribute to achieve better outcomes.

Conflicts of interest statement

Authors have no conflict of interest to disclose to the current manuscript.

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Contributions. Y.E., S.T., A.T., S.A., and K.T. designed the study; Y.E., S.M., S.K., T.K., and J.O. performed patients' care; K.Y. and F.N. analyzed data statistically; and Y.E. and K.T. wrote the paper.

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RESEARCH METHODOLOGY

Stressor Scale for Clinical Research Coordinators: development and psychometric testing

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Abstract

Aim. This article is a report of the development and psychometric testing of the Stressor Scale for Clinical Research Coordinators.

Background. Job stress is viewed as a situation where working conditions interact with individual worker characteristics and result in disruption of psychological or physiological homeostasis. Clinical research coordinators, also known as research nurses, are professionals who play a central role in clinical trials. They face various problems associated with their responsibilities; however, few studies have reported on their stress. To manage their stress, it is necessary to identify the sources of stress (i.e. stressors).

Method. The 56-item preliminary instrument was developed based on literature review and expert discussions. A total of 589 clinical research coordinators in 186 hospitals in Japan were surveyed in 2011. Statistical analyses on construct and concurrent validity, internal consistency, and test–retest reliability were performed.

Results. A six-factor solution with 23 items was selected using exploratory factor analysis: 'quantitative workload', 'conflict with investigators', 'ambiguity of work', 'conflict with other clinical research coordinators and with supervisors', 'demands from an affiliate other than the hospital', and 'difficulty in caring for trial participants'. Confirmatory factor analysis affirmed construct validity, with a demonstrated acceptable fit between the factor structure and the observed data. All factors had significant correlations with burnout and psychological distress, which indicated acceptable concurrent validity. Cronbach's alpha coefficients ranged from 0·73–0·82. Intra-class correlation coefficients indicated almost satisfactory test–retest reliability.

Conclusion. Our new instrument has acceptable validity and reliability for evaluating job stressors for clinical research coordinators.

Keywords: clinical research coordinators, clinical trials as topic, instrument development, nurses, occupational health, psychometric testing, stress

Introduction

Job stress is viewed as a situation in which working conditions interact with individual worker characteristics and result in acute disruption of psychological or physiological homeostasis (Hurrell & Murphy 1992, p. 676). There are a vast number of studies on stress among healthcare professionals, indicating that the levels of job stress among these professionals may be high (Michie & Williams 2003, Marine *et al.* 2006).

Clinical research coordinators (CRCs), also known as research nurses, are relatively newly formed professionals who play a central role in conducting clinical trials appropriately. Major CRC responsibilities include assistance with protocol submissions; participant recruitment; acquisition of informed consent; coordination of participant visits; collection and maintenance of clinical data; and serving as the main liaison between participants, investigators and sponsors (Davis *et al.* 2002). The daily conduct of any clinical trial depends on the performance of CRCs (Eaton & Pratt 1990).

The number of CRCs has increased internationally because of the increasing numbers of clinical trials (Spilsbury *et al.* 2008). The international societies for CRCs, such as the Society of Clinical Research Associates and the Association of Clinical Research Professionals, have been established, and the number of CRCs participating in them has continued to rise.

The literature indicates that CRCs face various problems in their work; however, reports addressing the job stress of CRCs are few. It is first necessary to evaluate their sources of stress (i.e. stressors) by a validated instrument to address the stress management of CRCs. The Stressor Scale of Clinical Research Coordinators (SSCRC) was designed to measure job stressors of CRCs based on National Institute for Occupational Safety and Health (NIOSH) job stress model (Hurrell & McLaney 1988, Hurrell & Murphy 1992).

Background

Mueller and Mamo (2002) reported three themes in CRCs facing problems: work autonomy/control, relationship with patients and with doctors, and clinical or technical skill and knowledge. Hoglund *et al.* (2010) showed CRCs' ethical dilemmas such as conflict between their obligations to clinical trials and those to participants. Other studies highlighted the problems of workload, multitasking, feelings of isolation, job control, working with patients, collaboration with other healthcare professionals and uncertain career development (Fisher 2006, Hill & MacArthur 2006, Roberts *et al.* 2006, Rickard *et al.* 2007, Spilsbury *et al.* 2008, Granda *et al.* 2009). Moreover, burnout in CRCs is comparable to levels reported by other healthcare professionals (Gwede *et al.* 2005). From these studies, it would seem apparent that CRCs' work environment is stressful because of broadly defined roles and the relatively new CRC specialty.

The NIOSH job stress model is composed of stressors, stress reactions, and three other factors (individual factors, non-work factors and buffer factors) (Hurrell & McLaney 1988, Hurrell & Murphy 1992). Stressors lead to physical, psychological and behavioural stress reactions. In this model, importance of focusing on stressors on stress management strategy is emphasized. Thus, a way to identify and intervene in the job stressors for individual workers is needed.

Various instruments have been used to measure stressors. Some of these instruments, such as the generic job stress questionnaire (Hurrell & McLaney 1988) and the job content questionnaire (Karasek 1985), were designed to be adapted for any occupation. However, the limitation of measuring stressors of specific occupational groups is that various occupational groups may differ in the nature of their work environment, and they may be exposed to different stressors (Senol-Durak *et al.* 2006). Correspondingly, occupation-specific instruments targeted at specific professions, including clinical nurses (Gray-Toft & Anderson 1981) and mental health professionals (Cushway *et al.* 1996), have been developed.

A validated instrument that measures the stressors for CRCs has not yet been developed; a valid and reliable instrument that measures the stressors specific to CRCs is important in improving stress reduction interventions and in promoting quality clinical trials across various countries.

The study

Aim

The aim of this study was to develop and test the psychometric properties of the Stressor Scale for Clinical Research Coordinators (SSCRC).

Methodology

The SSCRC was developed and tested in two stages as described below.

Stage 1: Item generation and content validation

Items were developed based on a literature review. We identified the literature related to the role and potential stressors of CRCs, and existing occupational-specific or nonspecific stressor instruments using PubMed, CINAHL, Web of

Science, and Ichushi-Web (in Japanese). After reviewing all the articles, we categorized seven hypothetical conceptual domains of stressors: conflict within clinical trial team, quantitative workload, role ambiguity, conflict with other CRCs and with supervisors, difficulty in caring for trial participants, qualitative workload and work environment and structure. The preliminary 61 items based on these domains were developed simultaneously. Next, we discussed the content validity with experienced CRCs, expert doctors in clinical trials and nurse researchers. Based on discussions, some of the items were combined or modified. Finally, a list of 56 items for SSCRC was created. The scale asked CRCs: 'Please select the response options below that best describe your daily work as a CRC regarding each question'. The items were assessed using a five-point Likert scale ranging from 1, 'strongly disagree',–5, 'strongly agree' with higher scores indicating a higher stressor. We used this 56-item SSCRC in Stage 2.

Stage 2: Test of psychometric properties

Participants

We contacted 325 hospitals that were registered with Massive Network for Clinical Trials (The Japan Medical Association 2010) and six hospitals that were designated either Core Clinical Research Centers or Major Clinical Trial Institutions (Ministry of Health, Labor and Welfare 2007) in Japan by mail in November 2010 to ask the current number of CRCs. Of the 331 hospitals, 239 responded with the number of CRCs, and 28 were excluded because they did not employ CRCs. The total number of participants was 1,033 CRCs from 211 hospitals. We mailed questionnaires in January 2011. To examine test–retest reliability, we sent the second questionnaire 3 weeks later.

Instrument

In addition to the 56-item SSCRC, we used the Mashlach Burnout Inventory-General Survey (MBI-GS) and K6 to examine concurrent validity of SSCRC. The MBI-GS is a seven-point Likert scale that measures burnout (Maslach *et al.* 1996, Kitaoka-Higashiguchi *et al.* 2004). MBI-GS includes three subscales: exhaustion, cynicism, and professional efficacy. However, we used only exhaustion and cynicism subscales because they are related to job stressors, and there is no direct relationship between professional efficacy and stressors (Leiter 1991, Kitaoka-Higashiguchi 2005). Cronbach's alpha coefficients for the present sample were 0·91 and 0·83 for exhaustion and cynicism, respectively.

The K6 is a six-item screening instrument for psychological distress (Kessler *et al.* 2002, Furukawa *et al.* 2008). We used K6, because it is quick to complete and effective for detecting depressive and anxiety disorders (Furukawa *et al.* 2003). Cronbach's alpha coefficient for the present sample was 0·90.

Ethical considerations

A university ethics committee approved this study. All questionnaires were completed anonymously. Participant consent was confirmed by their completion of the questionnaire.

Data analysis

Data were analysed using R version 2.12.2 (R Development Core Team 2011). Questionnaires with missing data on items of SSCRC were excluded. Ceiling and floor effects were examined by assessing highly skewed items, defined as a mean ± 1SD beyond the scope of the variable (Tanimura *et al.* 2011).

Exploratory (EFA) and confirmatory factor analyses (CFA) were conducted to investigate the construct validity. We used the maximum likelihood method EFA with a promax rotation. The number of factors was determined using scree plot test, parallel analysis, minimum average partial criterion and interpretability (Velicer 1976, Floyd & Widaman 1995). As a result of the EFA, we eliminated items that did not meet the following criteria: (1) each item had a factor loading $>0{\cdot}5$ on a factor, (2) each item did not have loadings $>0{\cdot}25$ on multiple factors, (3) each factor contained three or more items. Following the EFA, factor structure of SSCRC was evaluated using the CFA. We hypothesized and tested a second-order factor model composed of the factors extracted by the EFA as first-order factors and the SSCRC as a second-order factor. The model fitness was assessed with the following fit indices: goodness of fit index (GFI), adjusted GFI (AGFI), comparative fit index (CFI) and root mean square error of approximation (RMSEA). GFI, AGFI and CFI values greater than 0·90 are acceptable fits, whereas values greater than 0·95 are good fits. An RMSEA of less than 0·10 indicates an acceptable fit, whereas one less than 0·05 indicates a good fit (Murohashi 2007). The analyses of EFA and CFA were conducted according to previous studies (Sanjo *et al.* 2009, Chen *et al.* 2011). To examine concurrent validity, we calculated Pearson's correlation coefficients for SSCRC with exhaustion and cynicism of MBI-GS and K6.

Multitrait scaling analysis was employed to examine convergent validity (item-own factor correlation $>0{\cdot}40$,

factor corrected for overlap) and discriminant validity (item-own factor correlation higher than item-other factor correlations) (Fayers & Machin 2000).

Cronbach's alpha was calculated to confirm internal consistency. Good internal consistency was defined as an alpha value exceeding 0·70 (Fayers & Machin 2000). To evaluate test–retest reliability, we calculated intra-class correlation coefficients (ICCs) for total score and each factor score, with a coefficient of 0·70 indicating acceptable test–retest reliability (Fayers & Machin 2000). A 3-week interval was chosen because 1–6-week intervals were used in previous studies on stressor scale development (Higashiguchi *et al.* 1998, Senol-Durak *et al.* 2006, Khader *et al.* 2009).

Results

A total of 643 questionnaires from 191 hospitals were returned, and 589 from 186 hospitals were analysed (response rate of 62·2% and effective response rate of 57·0%). Table 1 shows the demographic characteristics of the CRCs. Most respondents were female (85·7%), nurses (49·1%), and full-time employees (73·7%).

We eliminated three items from the 56-item SSCRC due to floor/ceiling effect. In the first EFA, we determined seven-factor model. Based on result of the first EFA, we eliminated 24 items due to low loading on one factor, four items due to high loadings on multiple factors, and one factor (containing two items) because its factor had only two items. The result of the second EFA of six-factor model with remaining 23 items met the above criteria (Table 2). The results of the CFA and the names of the factors are shown in Figure 1. The fit indices were approximately satisfactory (GFI = 0·910, AGFI = 0·889, CFI = 0·922, RMSEA = 0·054). All standardized coefficients in the model were moderate to high (0·52–0·86) with statistical significance ($P < 0·001$).

The results of concurrent validity and convergent and discriminant validity are presented in Table 3. The total score and all factors of SSCRC showed low-to-moderate correlations, with statistical significance with burnout and psychological distress. All items had acceptable convergent validity with item-own factor correlations above 0·40, and discriminant validity with item-other factor correlations lower than the item-own factor.

Table 4 shows internal consistency and test–retest reliability. Cronbach's alpha coefficient of the total scale was 0·88 and those of each factor ranged from 0·73–0·82. A total of 405 participants completed the retest. All factors except Factor 6 had acceptable test–retest reliability with the ICCs exceeding 0·70 (0·74–0·84); however, the ICC of Factor 6 was 0·65.

We computed average scale scores (sum of the item scores divided by the number of items) (Table 4). Factor 5 had the lowest average scale score (mean = 2·3), and Factor 1 had the highest average scale score (mean = 3·0).

Table 1 Personal and organizational demographic characteristics of the respondents (n = 589).

Personal demographics	
Age, mean (SD)	39·4 (8·2)
Gender	
Male	82 (13·9)
Female	505 (85·7)
Marital status	
Married	329 (55·9)
Single	224 (38·0)
Divorced/widowed	34 (5·8)
Medical licence	
Nurse	289 (49·1)
Pharmacist	228 (38·7)
Medical technologist	60 (10·2)
Other/nothing	11 (1·9)
Years of experience of CRC	
< 2	152 (25·8)
2– < 5	218 (37·0)
5– < 10	180 (30·6)
≤10	31 (5·3)
Employment status	
Full-time	434 (73·7)
Part-time	153 (26·0)
Number of clinical trials for the past year	
0–4	190 (32·3)
5–9	171 (29·0)
10–19	153 (26·0)
20–	45 (7·6)
Qualification of CRCs	
Yes	232 (39·5)
No	351 (59·7)
Organizational demographics	
Organization of the hospital	
University	237 (40·2)
National	157 (26·7)
Other	195 (33·1)
Number of beds in the hospital	
0–199	27 (4·6)
200–599	221 (37·5)
600–799	161 (27·3)
800–	180 (30·6)
Number of CRCs in the hospital	
1–2	46 (7·8)
3–5	181 (30·7)
6–9	148 (25·1)
10–	214 (36·3)

Values are given as n (%).
SD, standard deviation; CRC, clinical research coordinator.

Table 2 Exploratory factor analysis of the SSCRC: factor loadings and inter-factor correlations after promax rotation (n = 589).

Factor		Factor loadings					
		F1	F2	F3	F4	F5	F6
Factor 1: Quantitative workload							
Q1	I have to work a lot of overtime	**0·91**	−0·05	−0·08	0·03	−0·05	0·03
Q2	There is a great deal of work to be done	**0·82**	0·09	−0·03	−0·03	−0·01	0·04
Q3	I have to work nights, early mornings, or weekends	**0·65**	−0·15	−0·01	0·03	0·06	−0·06
Q4	My role is too broad	**0·60**	0·10	0·03	−0·08	0·04	0·03
Factor 2: Conflict with investigators							
Q5	I feel it is difficult to do my work because investigators do not execute their responsibilities	−0·01	**0·84**	−0·04	0·03	0·00	−0·04
Q6	Investigators do not provide me with necessary information when needed	−0·03	**0·77**	0·09	−0·03	−0·10	−0·06
Q7	I have difficulties obtaining enough time with investigators	0·01	**0·62**	0·04	−0·07	0·00	0·08
Q8	I have to work under a bad relationship between investigators and trial participants	−0·06	**0·54**	−0·03	0·06	0·03	0·08
Q9	Investigators make unilateral demands without considering my situation	0·13	**0·53**	−0·06	0·02	0·20	0·01
Factor 3: Ambiguity of work							
Q10	I am not certain about my contribution to the outcomes of clinical trials	−0·12	−0·11	**0·77**	−0·09	0·03	0·08
Q11	I am not certain about the desired role of CRCs	−0·11	0·06	**0·75**	−0·01	−0·05	0·02
Q12	I am not certain whether my current work leads to a future career	0·11	0·04	**0·58**	−0·04	−0·07	0·02
Q13	I do not receive sufficient support for my career development	0·16	0·03	**0·53**	0·04	0·01	−0·08
Q14	I do not have sufficient authority to perform clinical trials	0·02	0·07	**0·51**	0·16	0·04	−0·12
Factor 4: Conflict with other CRCs and with supervisors							
Q15	I do not want to work with a certain CRC and/or supervisor	0·02	−0·01	−0·10	**0·84**	−0·02	0·02
Q16	I have colleagues of CRCs and/or supervisor whose opinion on work is different from mine	−0·04	0·01	−0·01	**0·83**	0·02	0·07
Q17	I have to work with uncooperative CRCs and/or supervisor	0·03	0·01	0·12	**0·70**	−0·03	−0·06
Factor 5: Demands from an affiliate other than the hospital							
Q18	I face inadequate responses from an affiliate other than the hospital (e.g. Sponsor)	0·00	0·01	−0·05	0·00	**0·88**	−0·08
Q19	I have to treat the inadequate demand for participants from an affiliate other than the hospital (e.g. Sponsor)	0·01	−0·05	0·00	−0·02	**0·78**	0·03
Q20	I have to engage in clinical trials that I think are meaningless or worthless	−0·09	0·00	0·08	0·02	**0·58**	0·05
Factor 6: Difficulty in caring for trial participants							
Q21	I cannot sufficiently care for trial participants suffering from diseases or symptoms	0·07	−0·03	−0·09	0·02	−0·04	**0·76**
Q22	I feel there are difficulties explaining in a way that trial participants can understand well	−0·03	0·07	0·05	0·02	−0·10	**0·67**
Q23	I cannot fully respond to anxiety or demands of trial participants	0·03	−0·12	0·16	0·03	0·09	**0·63**
Inter-factor correlations							
Factor 1		1·00	0·40	0·39	0·36	0·54	0·18
Factor 2		0·40	1·00	0·59	0·42	0·51	0·45
Factor 3		0·39	0·59	1·00	0·53	0·50	0·39
Factor 4		0·36	0·42	0·53	1·00	0·45	0·12
Factor 5		0·54	0·51	0·50	0·45	1·00	0·34
Factor 6		0·18	0·45	0·39	0·12	0·34	1·00

Bold values are the items assigned to the factor.

Discussion

Study limitations

First, the effective response rate of 57·0% is somewhat lower than that in several studies [e.g. 77% in Khader *et al.* (2009) and 65% in Rout (2000)]. However, the effect on this study was not crucial, because sufficient data were collected from major hospitals nationwide. Second, this study was conducted in a single country. Although the role of CRCs is not considered to be very different between Japan and other countries (Aotani & Saito 2008), medical systems and professional backgrounds of CRCs may differ. In fact, the proportion of full-time CRCs in this study, at 73·7%, was

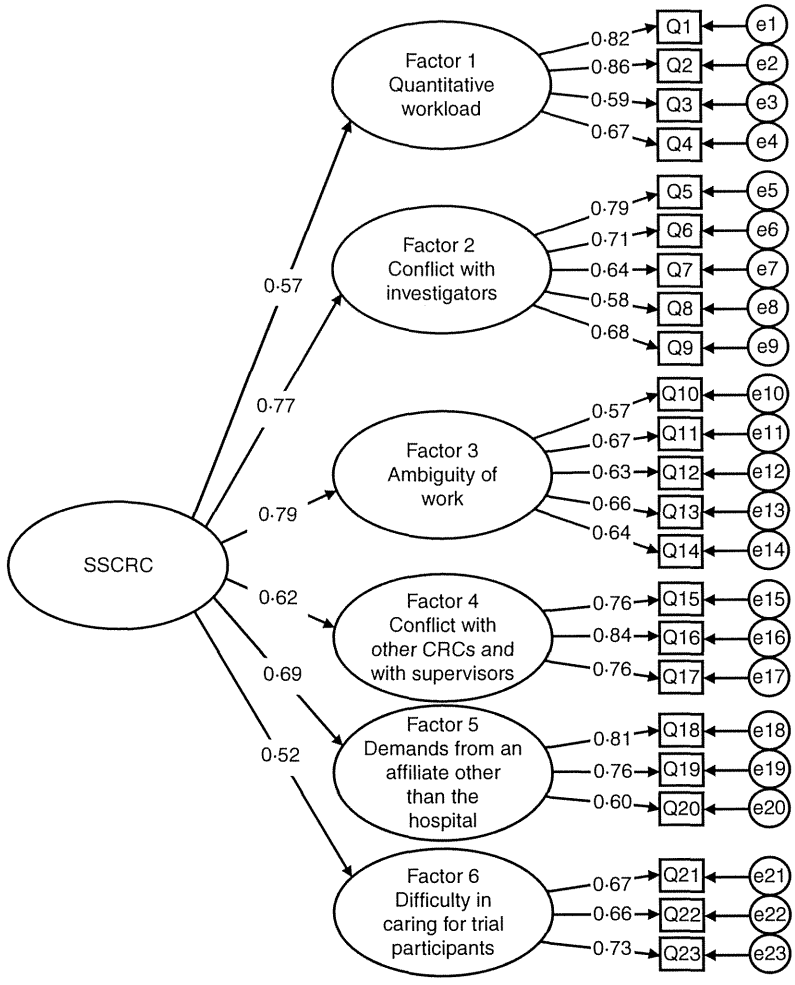

Figure 1 Confirmatory factor analysis of the SSCRC. CRCs, clinical research coordinators. Goodness of fit index = 0·910, adjusted goodness of fit index = 0·889, comparative fit index = 0·922, root mean square error of approximation = 0·054. All standardized coefficients were statistically significant ($P < 0·001$).

Table 3 Concurrent validity and convergent/discriminant validity of the SSCRC.

	Concurrent validity			Convergent validity†	Discriminant validity‡
	Exhaustion ($n = 560$)	Cynicism ($n = 560$)	K6 ($n = 587$)	Multitrait scaling analysis ($n = 589$)	
Total SSCRC	0·55**	0·48**	0·53**	0·50–0·74	0·03–0·45
Factor 1: Quantitative workload	0·45**	0·20**	0·32**	0·55–0·74	0·03–0·40
Factor 2: Conflict with investigators	0·35**	0·33**	0·33**	0·52–0·70	0·17–0·45
Factor 3: Ambiguity of work	0·35**	0·41**	0·42**	0·50–0·58	0·11–0·42
Factor 4: Conflict with other CRCs and with supervisors	0·40**	0·44**	0·45**	0·66–0·72	0·08–0·42
Factor 5: Demands from an affiliate other than the hospital	0·40**	0·35**	0·37**	0·51–0·66	0·18–0·41
Factor 6: Difficulty in caring for trial participants	0·23**	0·24**	0·25**	0·54–0·56	0·06–0·35

†Range of item-own scale correlation coefficients, corrected for overlap.
‡Range of item-other scale correlation coefficients.
**$P < 0.01$.

different from that in previous studies (Gwede *et al.* 2005, Rickard *et al.* 2007). Additional studies on the cross-cultural utility of SSCRC are encouraged, since regional differences may affect the stressors for CRCs.

Contents and structure of SSCRC

The SSCRC is based on a comprehensive literature review and discussions with experts, as emphasized by Streiner and