Table 3. Multivariate Analyses of Neutrophil and Platelet Recovery

			Neutrophil Recovery			Platelet Recovery		
	Degree of HLA Mismatch	N	RR	(95% CI)	P value	RR	(95% CI)	P value
Bone marrow transplantation	Single DRB1 (7/8)	248	1.00			1.00		
	Single A or B (7/8)	137	1.31	(1.04-1.65)	.021	1.31	(1.01-1.70)	.039
	Single C (7/8)	287	1.19	(0.98-1.43)	.069	0.98	(0.79-1.21)	.840
	C + DRB1 (6/8)	144	0.96	(0.77-1.20)	.735	0.79	(0.62-1.02)	.065
	A/B + C (6/8)	122	1.14	(0.89-1.45)	.307	0.84	(0.63-1.13)	.255
	Other two loci (6/8)	90	0.89	(0.68-1.14)	.346	0.80	(0.58-1.10)	.174
Cord blood transplantation		351	0.50	(0.42-0.60)	<.001	0.52	(0.42-0.63)	<.001

RR indicates relative risk; CI, confidence interval.
Adjusted by patient age at transplantation >40 versus <40, patient sex, donor-patient sex mismatch versus matched, ABO major mismatch versus others, advanced versus standard disease status at transplant, cyclophosphamide, and total-body irradiation or busulfan and cyclophosphamide for conditioning versus other conditioning regimen, and cyclosporine-based versus tacrolimus-based prophylaxis against graft-versus-host disease.

CI, 0.42-0.60; $P < .001$ for neutrophil recovery, RR = 0.52, 95% CI, 0.42-0.63; $P < .001$ for platelet recovery).

Acute GVHD and chronic GVHD

The risk of grade 2 to 4 or severe (grades 3-4) aGVHD was lower in CB recipients than that of single HLA-DRB1-mismatched BM recipients (RR = 0.55, 95% CI, 0.42-0.72; $P < .001$ for grade 2 to 4 aGVHD and RR = 0.43, 95% CI, 0.27-0.58; $P < .001$ for severe aGVHD) (Table 4). Unadjusted cumulative incidence of severe aGVHD was 9% for CB, 19% for single HLA-DRB1-mismatched BM, 18% for single HLA class I-mismatched BM, and 22% for 6 of 8 BM at 100 days posttransplantation ($P < .001$ between CB and single HLA-DRB1-mismatched BM) (Figure 2A).

Among recipients who survived at least 100 days posttransplantaton, the risk of developing cGVHD and extensive-type cGVHD was not significantly increased in all HLA disparity groups of CB recipients when compared with that of HLA-DRB1-allele/antigen-mismatched BM recipients (RR = 1.36, 95% CI, 0.99-1.88; $P = .057$ for cGVHD, and RR = 0.86, 95% CI, 0.55-1.34; $P = .500$ for extensive-type cGVHD). The unadjusted cumulative incidence of extensive-type cGVHD was 17% for CB recipients, 20% for single HLA-DRB1-mismatched BM, 25% for single HLA class I-mismatched BM, and 30% for 6 of 8 BM recipients at year posttransplantation ($P = .34$ between CB and single HLA-DRB1-mismatched BM) (Figure 2B).

DISCUSSION

Our main objective was to compare OS after transplantation of UCBT and single-HLA-mismatched UBMT and to provide useful data for selection of an appropriate donor and graft source in second stem cell source/donor selection for adults with hematologic malignancy. To the best of our knowledge, this is the first study to involve mismatched allele/antigen-specific analyses including CB for the process of donor selection. Our results suggest that 0 to 2 HLA-mismatched UCB is a reasonable second alternative of choice for adult patients with leukemia, with similar survival to that of single DRB1-mismatched or other 7 of 8 UBM recipients, the current first choice for second alternative donor/stem cells.

Neutrophil and platelet recovery was slower in CB recipients than BM recipients, consistent with the results of previous reports [7-10,12]. This is the major limitation of the use of UCB, and several strategies have been studied to reduce the neutropenic period, such as screening for patients' pretransplantation anti-HLA antibodies and their specificity, transplantation of 2 UCB units if a single UCB unit with an adequate cell dose is not available, or direct infusion of UCB into bone marrow [22-26].

Despite higher HLA disparity at the antigen level (69% 2 antigen mismatch, 25% antigen mismatch, and 6% matched), UCB recipients showed lower incidence of severe aGVHD than single DRB1-mismatched UBM recipients, consistent with other reports that compared UCB with single-mismatched UBM (7 of 8) [8,11,12]. In our study, tacrolimus and short-term methotrexate were used preferentially in BM recipients, whereas cyclosporine A was used in 68% of CB recipients. Prior studies have shown reduced severe aGVHD with tacrolimus, and this difference may have underscored the improved aGVHD control of UCB over mismatched BM in unadjusted analyses [27,28]. It is likely that decreased risk of grade 2 to 4 aGVHD in UCB recipients contributed to decreased risk of TRM among UCB recipients.

Increasing the number of HLA mismatches from 7 of 8 to 6 of 8 was associated with an approximately 10% reduction in survival in UBM recipients, which was quite similar to the results from the National Marrow Donor Program [3]. Because we eliminated data from the first 3 pioneering years of unrelated BMT, most of the bone marrow recipients and donors were allele-typed for at least HLA-A, -B, and -DRB1 before transplantation. Survival outcomes of single

Table 4. Multivariate Analyses of Acute (Grades 2 to 4 and Grades 3 to 4), Chronic, and Extensive-Type Chronic Graft-versus-Host Disease

	Degree of HLA Mismatch	N	Grade 2-4 acute GVHD			Grade 3-4 acute GVHD			Chronic GVHD			Extensive cGVHD		
			RR	(95% CI)	*P*-value	RR	(95% CI)	*P*-value	N	RR	(95% CI)	*P*-value	RR	(95% CI)	*P* value
Bone marrow transplantation	Single DRB1 (7/8)	248	1.00			1.00			199	1.00			1.00		
	Single A or B (7/8)	137	0.76	(0.55-1.06)	.103	0.91	(0.56-1.47)	.698	111	0.91	(0.61-1.36)	.646	0.89	(0.52-1.50)	.651
	Single C (7/8)	287	0.93	(0.72-1.20)	.584	0.91	(0.61-1.35)	.635	227	1.56	(1.15-2.10)	.004	1.79	(1.22-2.63)	.003
	C + DRB1 (6/8)	144	0.85	(0.60-1.18)	.320	0.88	(0.54-1.44)	.610	109	1.44	(1.01-2.05)	.041	1.47	(0.93-2.32)	.097
	A/B + C (6/8)	122	1.40	(1.04-1.90)	.028	1.90	(1.25-2.87)	.003	87	1.64	(1.14-2.34)	.007	2.26	(1.46-3.50)	<.001
	Other two loci (6/8)	90	0.88	(0.60-1.28)	.501	0.65	(0.34-1.22)	.183	60	1.35	(0.86-2.12)	.191	1.15	(0.62-2.13)	.652
Cord blood transplantation		351	0.55	(0.42-0.72)	<.001	0.43	(0.27-0.58)	<.001	252	1.36	(0.99-1.88)	.057	0.86	(0.55-1.34)	.500

GVHD indicates graft-versus-host disease; cGVHD, chronic graft-versus-host disease.
Adjusted by patient age at transplantation >40 versus <40, patient sex, donor-patient sex mismatch versus matched, ABO major mismatch versus others, advanced versus standard disease status at transplantation, cyclophosphamide, and total-body irradiation or busulfan and cyclophosphamide for conditioning versus other conditioning regimen, and cyclosporine-based versus tacrolimus-based prophylaxis against graft-versus-host disease.

class I mismatch were not significantly different from those of single class II mismatch in the current analyses. We believe that allele typing of HLA-A, -B, and -DRB1 before transplantation led to better selection of the donor compared with that in the first several years of UBMT. This study includes a large number of fully typed BM and CB recipients, but there are limitations. The choice of stem cell source is influenced by many unmeasured factors that can affect outcome. It is also influenced by the availability of acceptable HLA disparity for unrelated donors and mainly cell dose for cord blood units. Although we have adjusted for known risk factors and disparities between groups, we cannot rule out the influence of potential selection bias, which can only be excluded in a randomized controlled trial. Transplantation years of UBM recipients included from 1996 and 1999, for which there were no significant outcome differences between UBMT performed in 1996 to 1999 and after 2000. In these periods, there were advances including in supportive care and nutritional management, introduction of new antifungal agents, and more frequent use of tacrolimus, which may have affected transplantation outcomes [27-32].

In conclusion, we suggest that 0 or 2 HLA-mismatched UCB is a comparable second alternative

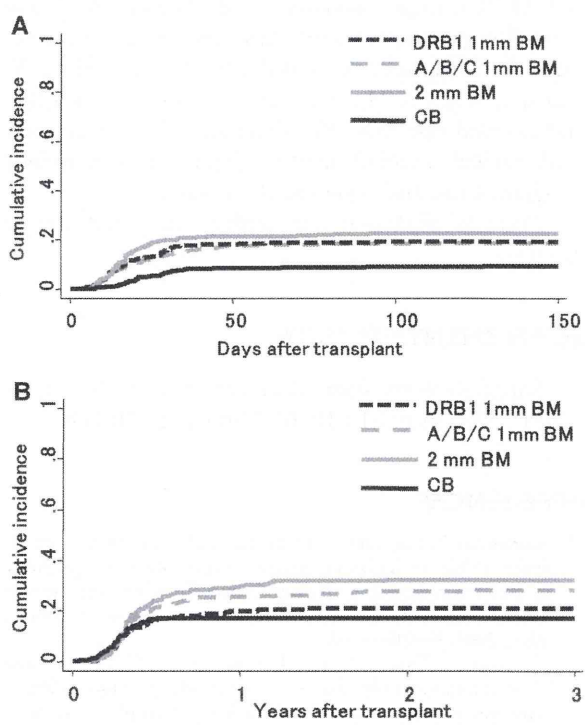

Figure 2. Cumulative incidence of grade 3 to 4 aGVHD (**A**) and extensive-type cGVHD (**B**). The cumulative incidences of grade 3 to 4 aGVHD at 100 days posttransplantation for unrelated cord blood recipients, single HLA-DRB1-mismatched unrelated bone marrow (UBM) recipients, and single HLA class I-mismatched UBM were 9%, 19%, 18%, and 22% (**A**). The cumulative incidences of extensive-type cGVHD at 1-year posttransplantation were 17%, 20%, 25%, and 30% (**B**).

for adult patients with leukemia in the absence of the first alternative, an 8 of 8 UBM donor, with survival similar to that of single DRB1-mismatched or other 7 of 8 UBM recipients. UCB may be preferred over single mismatched UBM when a transplantation is needed urgently, considering the short time needed for UCBT.

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AUTHORSHIP STATEMENT

Contributions: Y.A., Y.M., R.S., and S. Kato designed the study, and wrote the article; Y.A. analyzed results and created the figures; T.N.I., H.A, and M. Takanashi reviewed and cleaned the Japan Cord Blood Bank Network data, and reviewed the results; S. Taniguchi, S. Takahashi, S. Kai., H.S., Y. Kouzai., N.K., T.M., T.F., and Y. Kodera submitted and cleaned the data; M. Tsuchida, K.K., T.K., and Y.M. reviewed and cleaned the Japan Marrow Donor Program data, and reviewed the results.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2011.10.008.

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—【報　告】— Report —

院内における血液細胞処理のための指針

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既に治療法として確立している造血幹細胞移植に用いる細胞処理のガイドラインを，日本輸血・細胞治療学会と日本造血細胞移植学会との共同指針として今回初めて策定した．欧米の FACT-JACIE 基準を参考にする一方で，移植施設が小規模で分散し移植に係るコメディカルの少ないわが国の状況を踏まえて，多くの施設が受容し得る内容とした．ただし，必ずしも現在の大半の施設が満たす基準ではなく「目指すべき基準（理想的な基準）」の内容も含めた．構成は，1 目的，2 対象，3 細胞の採取，4 責任者と作業者，5 設備・機器，6 細胞処理（プロセシング），7 払い出し，8 保存と解凍，9 検体保存，10 投与，11 廃棄，12 雑則からなり，教育的観点から「付」として代表的な細胞処理法に関して，解説，標準作業手順書(SOP)サンプル，記録シートサンプル，結果シートサンプルなどを設けた．今後この指針が多くの場面で運用されるように努めるとともに，現場に即した指針となるように改訂を重ねていく必要がある．また，将来的に欧米の最新の指針と同等の基準となり，また輸血・細胞処理部門認定や有害事象の監視体制を構築するのに活用されることが期待される．

キーワード：造血幹細胞移植，細胞処理，指針，SOP

はじめに

医療施設内で処理・製造される洗浄血小板や造血幹細胞等の院内血液細胞製剤は輸血医療や細胞治療にいまや不可欠である．しかしながら，これらの院内製剤は，Good Manufacturing Practice（GMP）の下で日本赤十字社等から供給される血液製剤[1)2)]と異なり，その安全性や品質の保証は担保されていない．従って，院内血液細胞製剤の扱いは，血液法のもと行政に残された喫緊の課題である．そこで，院内血液細胞製剤を扱う国内のあらゆる施設が遵守すべき最小限の基準をここに作成し，血液細胞製剤(生物製剤，生物由来製品，臨床研究用細胞・組織製剤等）における院内血液細胞製剤の規制上の位置づけを明確にするとともに，血液法に則り，院内血液製剤の安全性の向上，適正使用の推進，そして安定供給の確保への行政ならびに医療機関の取り組みを促すことを目標とする[3)4)]．

本基準は，日本輸血・細胞治療学会が主体となり日本造血細胞移植学会の協力を得て作成された．また，FACT-JACIE2006 年第 3 版(Part C および D)[5)]を参考とした．ただし，輸血・細胞処理部門のわが国の現状

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5）藤田保健衛生大学血液化学療法科
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8）慶應義塾大学病院輸血・細胞療法部
9）ニューヨーク血液センター細胞治療研究開発室
10）福島県立医科大学輸血移植免疫学
〔受付日：2010 年 10 月 15 日，受理日：2010 年 12 月 9 日〕

を考慮し[6]，必ずしも多くの施設が満たす基準ではなく「目指すべき基準」の内容も含めた．これに関しては，文末に「望ましい」という表現で示した．指針は本文部分に加え，「付」として，代表的な細胞処理についての解説，標準作業手順書（standard operating procedures；SOP）サンプル，記録用紙サンプル，結果用紙サンプルなどを提示した（http://www.jstmct.or.jp/jstmct/Guideline/List.aspx）．

今後，特に欧米の指針と同等の基準となるべく，改定を加えることができるようにする．また，将来的に輸血・細胞処理部門認定や有害事象の監視体制を構築することも可能と考えられる．

指針本文概要

1　目的

本基準は，細胞の性状を変えることなく医療施設内で処理・製造される院内血液細胞（以下，「血液細胞製剤」と称し，主に造血幹細胞等を意味する）の製造工程において，安全で高い品質を確保し，また製剤に問題があった場合に原因等の遡及調査を可能にすることを目的とする．

2　対象

主に造血幹細胞移植に関連して院内で実施される細胞採取・処理・凍結保管を本指針の対象とする．すなわち，①同種および自家末梢血幹細胞の凍結保存と解凍，②同種および自家骨髄の赤血球除去，血漿除去および単核球の分離，凍結保存と解凍，③ドナーリンパ球輸注（donor lymphocyte infusion；DLI）のためのリンパ球の採取・凍結保存と解凍，④臍帯血移植における細胞保存と解凍．ただし，臨床研究として行われる細胞療法や再生治療に関わる細胞処理は対象としない．なお，上記の処理を院内で実施する全ての病院を本指針の対象とする．

3　細胞の採取

採取施設は以下の規定に従うこと．すなわち，非血縁者骨髄採取は骨髄バンクの「ドナー適格性判定基準」と「骨髄採取マニュアル」を遵守する．末梢血幹細胞採取では「末梢血幹細胞動員・採取に関するガイドライン」（日本造血細胞移植学会，日本輸血・細胞治療学会）を遵守する．非血縁ドナーDLIでは「ドナーリンパ球輸注（DLI）コーディネートマニュアル」（骨髄バンク）を遵守する．血縁ドナーもこれらに準ずることが望ましい．血縁ドナーでは必ず採取前に「血縁造血幹細胞ドナー（骨髄/末梢血）団体傷害保険」の説明を行うこと．

4　責任者と作業者

責任体制を明確にするため，総括責任者，細胞採取責任者，細胞処理責任者，品質管理責任者をおくこと．各責任者はそれぞれ別が望ましいが兼任可能とする．総括責任者は製造された血液細胞製剤を用いて治療を行う診療科長・部長等の医師で，これらの基準が適切に運用されるよう努めること．細胞採取責任者は細胞採取に習熟した医師で，細胞が適切に採取されるよう努め，適宜作業者の教育を行うこと．細胞処理責任者は細胞処理に習熟した医師で，細胞が適切に処理・管理されるよう努め，適宜作業者の教育を行うこと．品質管理責任者はこれらの基準が適切に運用されるよう体制を整え維持し，適宜作業者の教育を行うこと．作業者は予め細胞プロセッシングに係る十分な教育訓練を受け，全ての工程に習熟していること．

5　設備・機器

閉鎖系で細胞処理を行う場合は専用の機器を用いること．開放系で行う場合はクリーンベンチなどを完備する．設備と機器は定期的に点検を行い，その記録を保管すること．

6　細胞処理（プロセシング）

細胞処理を行う場所は，照明，換気，給排水が整備され，十分広く清潔で専用とし，部外者の立ち入りが制限され，必要な機器や物品が機能的に配置されていることが望ましい．複数の検体を同じ場所で同時に扱わず，出庫前の製剤を保管する場所を設置することが望ましい．

安全管理のため，作業者等の危険性を最小限にするよう配慮すること．作業中は手袋，ヘアーキャップ，マスク，専用衣を着用し，伝染性微生物，有害な化学薬品，放射性危険物に作業者が暴露した場合の対応方法を安全マニュアルに整備すること．医療廃棄物は適切に処理すること．

細胞処理では各作業のSOPを整備すること．SOPには目的，機器と消耗品，作業工程，指示書，工程記録等を含むことが望ましい．担当者はSOPをいつでも参照できること．新規・改定では責任者が事前に内容を確認すること．特定生物由来製品を使用した場合，薬事法で定める事項を記録し20年間保存すること．

担当医からの申込書等があること．凍結した場合は解凍後の生細胞率を評価することが望ましい．工程手順が新規・改定された場合は，事前にテストランを行うことが望ましい．処理は無菌的に行い，開放系での処理はクリーンベンチ内等で実施すること．作業工程記録書を作成し記録することが望ましい．重要な試薬，消耗品のロット番号，使用期限，重要な機器の種類等を記載すること．検査として，総有核細胞数と生細胞率（凍結した場合），末梢血幹細胞のCD34陽性細胞数，細菌・真菌検査を含むことが望ましい．菌検査が陽性の場合は，責任者等に速やかに連絡し，事前に定めた対処法に準じて対応すること．出庫の基準を各施設で

定めること．検査方法や機器の保守・点検の検査も含むことが望ましい．

ラベルは取り違いのないように運用し，細胞等の受入・出庫には2人以上で照合すること．処理途中のバッグや検体にも識別番号，製剤名，採取日時等のラベルを貼付等すること．

7　払い出し

出庫までに細胞処理責任者は工程記録を審査すること．出庫時には2人以上で外観，ラベルや名前等を確認し，工程記録に記録することが望ましい．

8　保存と解凍

製剤を保存する場合は施錠等し，部外者の立ち入りは制限されていること．

製剤ごとに保管期間・温度等を定めること．保存庫は警報システム等により24時間対応できる体制であること．温度を継続的に記録できることが望ましい．完全に液体窒素内に浸された製剤では継続的な温度モニターは不要だが，液体窒素量を継続的に監視するシステムがあること．

血液細胞の解凍は37℃急速解凍を原則とする．解凍のためのSOP，工程記録を定めること．必要に応じて解凍サンプルの検査を行い，患者担当医に報告すること．

9　検体保存

処理後の細胞の一部を保存することが望ましい．検体には専用のラベルを貼付し専用の台帳で管理すること．

10　投与

輸血・細胞処理部門から搬送された製剤は，原則として担当医が速やかに患者に投与すること．患者への投与前に，担当医および看護師は，ベッドサイド等で，輸血製剤に準じた方法で指示書と患者氏名，ドナー氏名，ID，製剤名，採取日，容量等の照合をすること．

11　廃棄

細胞廃棄の基準を定め，予め廃棄承諾書をドナー（および患者）から得ること．

12　雑則

この指針は，細胞療法の進歩や医学的，社会的情勢の変化等を勘案して，必要に応じ，又は施行後5年を目途として見直しを行うものとする．なお，この指針は平成22年5月27日より施行する．

考　案

既に確立している造血幹細胞移植に用いる細胞処理について，日本造血細胞移植学会と日本輸血・細胞治療学会の共同指針を初めて策定した．従来，移植に用いられる細胞に関しては法的規制も学会指針もなかった．たとえば自家末梢血幹細胞移植は難治性悪性リンパ腫などの治療法として小規模病院でも実地臨床として行われるが[6]，細胞処理には専門の技術・管理が必要で，重大な事故が起こり得る．この工程を管理することは，最終産物の質を担保するだけでなく，これに係る医療従事者の責任も保証することでもあり，その必要性は自明である．

欧米では既に国レベルで細胞処理を規制・管理している[5]．わが国では移植施設が小規模で分散している点が欧米と異なり，施設によっては少数の血液内科医が不十分な設備で移植を何とかこなして地域医療に貢献していることもある[6]．指針策定の目的は，各施設でSOPを整備して再現性・計画性のある細胞処理・管理が行われること，処理工程や結果が適切に記録され必要時に遡及調査が可能なこと，責任体制を明確化することである．一方，グローバル化した現代においては欧米のFACT-JACIE基準[5]とも整合性を保つ必要がある．最終的に，これらさまざまな立場の関係者が受容し得る指針を作成した．このためには，複数の施設の移植に携わる医師および臨床検査技師からなる小委員会で原案を作成し，関連学会・シンポジウムなどで検討を重ね，さらに日本輸血・細胞治療学会および日本造血細胞移植学会のホームページでパブリックコメントを求めて最終版を作成した．今後これが多くの場面で運用されるように努めるとともに，現場に即した指針となるように改訂を重ねていく必要がある．

謝辞：本指針策定に際しては，日本輸血・細胞治療学会細胞治療委員会および日本造血細胞治療学会ガイドライン委員会の委員をはじめとして多くの先生方の御意見を参考にさせていただきましたことを深謝いたします．なお，本研究は厚生労働省科学研究費補助金（H20-医薬-一般-006）の補助を受けた．

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GUIDELINE FOR PROCESSING CELLULAR THERAPY PRODUCTS ROUTINELY USED FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN JAPAN

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Abstract:

In Japan, about 4,000 hematopoietic stem cell transplantations (HSCT) are currently performed for various hematologic and non-hematologic disorders in about 200 hospitals per year. However, there have been no regulations or professional standards or guidelines for the processing of cellular therapy products routinely used for HSCT. Therefore, the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT), in collaboration with the Japan Society for Hematopoietic Cell Transplantation (JSHCT), have established guideline, titled 'the Japanese Standards for Processing Cellular Therapy Products Routinely Used for Hematopoietic Stem Cell Transplantation', for all hospitals and related personnel performing HSCT. According to a nation-wide survey performed by JSTMCT, it is likely that the number of medical staff and equipment is insufficient in many hospitals. Although these guidelines are based on the world-wide standard, the FACT-JACIE 3rd edition, and are intended to be minimum standards, some modifications were made to reflect the present situation of most hospitals. The guidelines include; 1 Objective, 2 Application, 3 Product Collection, 4 Personnel, 5 Equipment and Facility, 6 Policies and Procedures, 7 Distribution, 8 Storage and Thawing, 9 Sample Storage, 10 Infusion, 11 Disposal, and 12 Provision. Appendices include outlines of each procedure related to transplantation and examples of standard operation procedures (SOPs) and record forms. The established standards are to be uploaded to the JSTMCT website so that individuals can access and download the SOPs and record forms, which can be revised for use at each hospital. An accreditation system is also planned to be established in the near future.

Keywords:

hematopoietic stem cell transplantation, cell processing, guideline, SOP

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Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study

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Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study

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Allogeneic hematopoietic cell transplantation (HCT) is an effective treatment for adult T-cell leukemia (ATL), raising the question about the role of graft-versus-leukemia effect against ATL. In this study, we retrospectively analyzed the effects of acute and chronic graft-versus-host disease (GVHD) on overall survival, disease-associated mortality, and treatment-related mortality among 294 ATL patients who received allogeneic HCT and survived at least 30 days posttransplant with sustained engraftment. Multivariate analyses treating the occurrence of GVHD as a time-varying covariate demonstrated that the development of grade 1-2 acute GVHD was significantly associated with higher overall survival (hazard ratio [HR] for death, 0.65; $P = .018$) compared with the absence of acute GVHD. Occurrence of either grade 1-2 or grade 3-4 acute GVHD was associated with lower disease-associated mortality compared with the absence of acute GVHD, whereas grade 3-4 acute GVHD was associated with a higher risk for treatment-related mortality (HR, 3.50; $P < .001$). The development of extensive chronic GVHD was associated with higher treatment-related mortality (HR, 2.75; $P = .006$) compared with the absence of chronic GVHD. Collectively, these results indicate that the development of mild-to-moderate acute GVHD confers a lower risk of disease progression and a beneficial influence on survival of allografted patients with ATL. (*Blood*. 2012;119(9):2141-2148)

Introduction

Adult T-cell leukemia (ATL) is a mature T-cell neoplasm that is causally associated with a retrovirus designated human T-cell leukemia virus type I (HTLV-I).[1-4] HTLV-I is endemic in southwestern Japan, sub-Saharan Africa, the Caribbean Basin, and South America.[3,4] In Japan, more than 1 million people were estimated to be infected with HTLV-I. Although the majority of HTLV-I–infected individuals remain asymptomatic throughout their lives, ~ 5% develop ATL at a median age of 40 to 60 years.[4,5]

ATL is categorized into 4 clinical variants according to its clinical features: smoldering, chronic, acute, and lymphoma types.[6] The acute and lymphoma variants of ATL have an extremely poor prognosis, mainly because of resistance to a variety of cytotoxic agents and susceptibility to opportunistic infections; the median survival time is ~ 13 months with conventional chemotherapy,[7,8] although encouraging results have been recently reported with the use of novel agents such as mogamulizumab.[9-11]

Over the past decade, allogeneic hematopoietic cell transplantation (HCT) has been increasingly performed with the aim of improving dismal prognosis of patients who developed ATL.[12-18] Notably, some patients with ATL who relapsed after allogeneic HCT were shown to achieve remission only with the cessation of immunosuppressive agents, raising the question of whether the graft-versus-leukemia effect against ATL can be induced as part of graft-versus-host reaction.[19,20] In 1 study, among 10 patients who experienced relapse of ATL after transplantation and were withdrawn from immunosuppressive therapy, 8 developed graft-versus-host disease (GVHD), and 6 of them subsequently achieved

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complete remission of ATL.[19] Similar observations have been rarely reported in other aggressive mature lymphoid neoplasms,[21] suggesting the unique susceptibility of ATL to graft-versus-host reactions. Recently, a combined analysis of 2 prospective studies including 29 ATL patients in total undergoing allogeneic HCT suggested that development of mild acute GVHD favorably affected overall survival and progression-free survival.[22] However, the impact of GVHD on the outcome of allogeneic HCT in ATL needs to be verified in a much larger cohort. We previously conducted a nationwide retrospective study to evaluate the current results of allogeneic HCT for ATL, and we confirmed that a substantial proportion of patients with ATL can enjoy long-term, disease-free survival after transplantation: the overall survival rate at 3 years among patients who received transplants in complete remission and not in complete remission was 51% and 26%, respectively.[23] Using the same cohort, we further evaluated the effects of acute and chronic GVHD on long-term outcomes of allografted patients with ATL.

Methods

Collection of data

Data on 417 patients with acute or lymphoma type ATL who had undergone allogeneic bone marrow, peripheral blood, or cord blood transplantation between January 1, 1996, and December 31, 2005, were collected through the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the Japan Marrow Donor Program (JMDP), and the Japan Cord Blood Bank Network (JCBBN), the 3 largest HCT registries in our country; their roles were detailed previously.[23] The patients were included from 102 transplant centers; the data were updated as of December 2008. The study was approved by the data management committees of JSHCT, JMDP, and JCBBN, as well as by the institutional review boards of Kyoto University Graduate School of Medicine, where this study was organized.

Inclusion and exclusion criteria

Patients were included in the analysis if the following data were available: age at transplantation, sex of the recipient, donor type, stem cell source, agents used in the conditioning regimen and GVHD prophylaxis, the maximum grade and day of occurrence of acute GVHD, and the day of neutrophil recovery. Acute GVHD was reported according to the traditional criteria,[24] except that 1 patient was considered to have late-onset acute GVHD at day 133; neutrophil recovery was considered to have occurred when an absolute neutrophil count exceeded 0.5×10^9/L for 3 consecutive days after transplantation. Patients who missed any of these data (n = 37), who had a history of prior autologous or allogeneic HCT (n = 8), who had received an ex vivo T cell–depleted graft (n = 1), who experienced primary or secondary graft failure (n = 24) were excluded from the analysis. Because the association between the occurrence of acute GVHD and disease-associated mortality was difficult to evaluate in the event of early toxic death, patients who died within 30 days of transplantation (n = 53) also were excluded from the study. Among these 53 patients, 22 were evaluable for acute GVHD: grade 0 in 17 patients, grade 1-2 in 3 patients, and grade 3-4 in 2 patients. Two physicians (J.K. and T.I.) independently reviewed the quality of collected data, and 294 patients in total (158 males and 136 females), with a median age of 51 years (range, 18-79 years), were found to meet these criteria and included in the study: 163 patients from JSHCT, 82 patients from JMDP, and 49 patients from JCBBN. No overlapping cases were identified. Of these 294 patients, the effects of chronic GVHD, reported and graded according to using traditional criteria,[25] were considered evaluable for the 183 patients who survived at least 100 days after transplantation with complete information on the type and the day of occurrence of chronic GVHD.

End points

The primary end point of the study was the effect of acute GVHD on overall survival, defined as the period from the date of transplantation until the date of death from any cause or the last follow-up. The secondary end points of the study included the impact of acute GVHD on disease-associated and treatment-related mortality, and the impact of chronic GVHD on overall survival, disease-associated mortality, and treatment-related mortality. Reported causes of death were reviewed and categorized into disease-associated or treatment-associated deaths. Disease-associated deaths were defined as deaths from relapse or progression of ATL, whereas treatment-related deaths were defined as any death other than disease-associated deaths.

Statistical analysis

The probability of overall survival was estimated by the Kaplan-Meier method. Treatment-related and disease-associated mortality were estimated with the use of cumulative incidence curves to accommodate the following competing events[26]: disease-associated death for treatment-related mortality and treatment-related deaths for disease-associated mortality. Data on patients who were alive at the time of last follow-up were censored. Semi-landmark plots were used to illustrate the effects of GVHD on overall survival and cumulative incidence of disease-associated and treatment-related deaths. For patients with acute or chronic GVHD, the probability of overall survival and the cumulative incidences of disease-associated and treatment-related deaths were plotted as a function of time from the onset of acute or chronic GVHD. Day 24.5, the median day of onset for acute GVHD, was termed as the landmark day in patients without acute GVHD. In the case of patients without chronic GVHD, day 116, the median day of onset for chronic GVHD, was termed as the landmark day.

Univariate and multivariate Cox proportional hazards regression models were used to evaluate variables potentially affecting overall survival, whereas the Fine and Gray proportional subdistribution hazards models were used to evaluate variables potentially affecting disease-associated and treatment-related mortality.[27] In these regression models, the occurrence of acute and chronic GVHD was treated as a time-varying covariate.[28] In the analysis of acute GVHD, patients were assigned to the "no acute GVHD group" at the time of transplantation and then transferred to the "grade 1-2 acute GVHD group" or to the "grade 3-4 acute GVHD group" at the onset of the maximum grade of acute GVHD. In the analysis of chronic GVHD, patients were assigned to the "no chronic GVHD group" at the time of transplantation and then transferred to the "limited chronic GVHD group" or to the "extensive chronic GVHD group" at the onset of the maximum grade of chronic GVHD. The variables considered were the age group of the recipient ($\leq$ 50 years or $>$ 50 years at transplantation), sex of the recipient (female or male), disease status before transplantation (complete remission, disease status other than complete remission, or unknown), intensity of conditioning regimen (myeloablative, reduced intensity, or unclassifiable), type of GVHD prophylaxis (cyclosporine-based, tacrolimus-based, or other), type of donor (HLA-matched related donor, HLA-mismatched related donor, unrelated donor for bone marrow, or unrelated cord blood), time from diagnosis to transplantation (within 6 months, $>$ 6 months, or unknown), and year of transplantation (1995-2002 or 2003-2005). We classified the intensity of conditioning regimen as myeloablative or reduced intensity based on the working definition by Center for International Blood and Marrow Transplant Research if data on dosage of agents and total-body irradiation (TBI) used in the conditioning regimen were available.[29] For 110 patients for whom such information was not fully available, we used the information on conditioning intensity (myeloablative or reduced intensity) reported by treating clinicians. The cutoff points for year of transplantation were chosen such that we could make optimal use of the data with a proviso that the smaller group contained at least 30% of patients. In the analysis of the effect of chronic GVHD, the prior history of grade 2-4 acute GVHD also was added to the multivariate models. We also assessed the interaction between acute GVHD and the intensity of conditioning regimen in the multivariate models. Only factors with a P value of less than .10 in univariate analysis were included in the multivariate models. In addition, the heterogeneities of the effects of grade 1-2 or grade 3-4 acute GVHD on overall survival according to background transplant characteristics were evaluated by the forest plots stratified by variables included in the regression analyses. Furthermore, landmark analysis treating the development of acute GVHD as a time-fixed covariate was performed to confirm

Table 1. Characteristics of patients and transplants

Variable	No. of patients, n = 294 (%)
Age group at transplant, y	
≤ 30	7 (2)
> 30-40	30 (10)
> 40-50	109 (37)
> 50-60	123 (42)
> 60	25 (9)
Sex	
Male	158 (54)
Female	136 (46)
Disease status	
Complete remission	99 (34)
Not in complete remission	178 (61)
Unknown	17 (6)
Conditioning regimen	
Myeloablative	102 (34)
Reduced intensity	128 (44)
Unclassifiable	64 (22)
GVHD prophylaxis*	
Cyclosporine-based	195 (66)
Tacrolimus-based	94 (32)
Other	5 (2)
Source of stem cells	
Bone marrow	132 (45)
Peripheral blood	111 (38)
Bone marrow + peripheral blood	2 (1)
Cord blood	49 (17)
Type of donor†	
HLA-matched related	132 (45)
HLA-mismatched related	31 (11)
Unrelated, bone marrow	82 (28)
Unrelated, cord blood	49 (17)
Time from diagnosis to transplant	
≤ 6 mo	141 (48)
> 6 mo	141 (48)
Uncertain/missing	12 (4)
Year of transplant	
1995-1999	22 (7)
2000-2002	91 (31)
2003-2005	181 (62)
Follow-up of survivors	
Median time, mo (range)	42.8 (1.5-102.3)

Data are numbers (%) unless specified otherwise.

*Cyclosporine-based indicates cyclosporine with or without other agents; tacrolimus-based indicates tacrolimus with or without other agents.

†HLA compatibility was defined according to the results of serologic or low-resolution molecular typing for HLA-A, B, and DR antigens.

the results of analyses treating the occurrence of acute GVHD as a time-varying covariate; the landmark day was set at day 68 after transplantation, the date until when more than 95% of patients developed acute GVHD.

Results are expressed as hazard ratios (HRs) and their 95% confidence intervals (CI). All tests were 2-sided, and a P value of less than .05 was considered to indicate statistical significance. All statistical analyses were performed with STATA Version 11 software (StataCorp).

Results

Characteristics of patients and transplants

Characteristics of the patients and transplants are shown in Table 1. Most of the patients received transplants at the age of 41 to 60 years (median, 51 years). The disease status at transplantation was mainly defined as other than complete remission. The intensity of conditioning regimen was classified as myeloablative in 102 (35%) patients and reduced intensity in 128 (44%) patients; the remaining 64 (22%) patients were reported to receive cyclophosphamide plus TBI in 16 patients; busulfan plus cyclophosphamide in 15 patients; busulfan plus melphalan in 1 patient; purine analog-containing regimen in 6 patients; and other TBI-based regimens in 26 patients, although the intensity of these regimens was considered unclassifiable because of lack of dosage information. Cyclosporine-based prophylaxis against GVHD was used in more than half of patients. Patients underwent transplantation using HLA-matched related donor in 132 patients (45%), HLA-mismatched related donor in 31 patients (11%), unrelated bone marrow donor in 82 patients (28%), and unrelated cord blood unit in 49 patients (17%). Half of the patients received transplants within 6 months of diagnosis. The median time of follow-up among the survivors was 42.8 months (range, 1.5-102.3 months).

Effects of acute GVHD on overall survival

The median onset day of acute GVHD of any grade after transplantation was 24.5 (range, 5-133). Acute GVHD of grades 1-4, 2-4, and 3-4 occurred in 202 patients (69%), 150 patients (51%), and 65 patients (22%), respectively. The effect of acute GVHD on overall survival was evaluated using semi-landmark plots with reference to the following 3 categories: no acute GVHD, grade 1-2 acute GVHD, and grade 3-4 acute GVHD (Figure 1A). The impact of grade 1-2 or grade 3-4 acute GVHD on overall survival also was evaluated by forest plots stratified by background characteristics of patients and transplants (Figure 2). These analyses revealed that development of grade 1-2 acute GVHD was consistently associated with higher overall survival compared with the absence of acute GVHD, whereas occurrence of grade 3-4 acute GVHD was consistently associated with lower overall survival, except that adverse impact of grade 3-4 acute GVHD was not observed in the subgroups of patients who received transplants from an HLA-matched related or HLA-mismatched related donor. Multivariate analysis treating an occurrence of acute GVHD as a time-dependent covariate also confirmed the positive impact of grade 1-2 acute GVHD (HR, 0.65; 95% CI, 0.45-0.93; P = .018) and the adverse impact of grade 3-4 acute GVHD on overall survival (HR, 1.64; 95% CI, 1.10-2.42; P = .014; Table 2). Patients who received reduced intensity conditioning and myeloablative conditioning had similar rates of overall survival by both univariate (HR of reduced intensity vs myeloablative transplant, 1.19; 95% CI, 0.85-1.68; P = .318) and multivariate analysis (HR, 0.95; 95% CI, 0.61-1.47; P = .814). There was no interaction effect between conditioning intensity and grade 1-2 (P = .704) or grade 3-4 acute GVHD (P = .891) on overall survival. The effect of each grade of acute GVHD on overall survival was additionally evaluated. It showed that only grade 2 acute GVHD was associated with superior overall survival, whereas only grade 4 acute GVHD was associated with inferior survival (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). In the landmark analysis treating an occurrence of acute GVHD as a time-fix covariate, consistent results were obtained for patients who survived at least 68 days (landmark day), although the adverse impact of grade 3-4 acute GVHD on overall survival became no longer significant (supplemental Table 2).

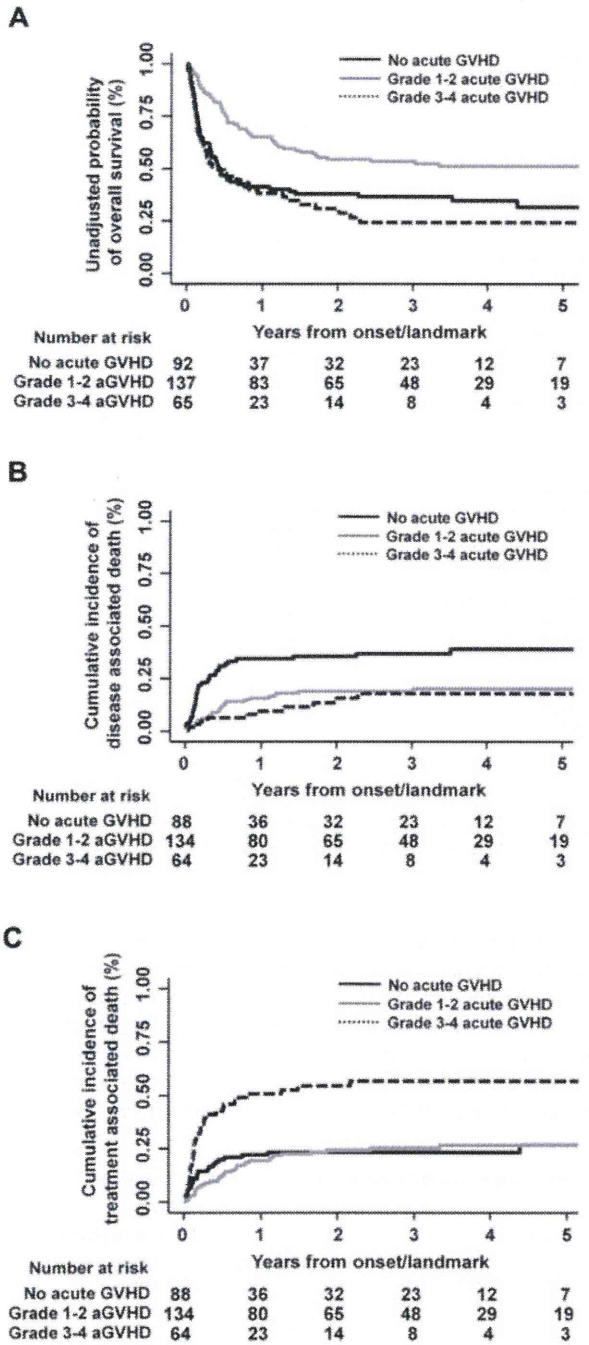

Figure 1. Semi-landmark plots for effects of acute GVHD. Semi-landmark plots illustrating the effects of acute GVHD on overall survival (A), disease-associated mortality (B), and treatment-related mortality (C).

Effects of acute GVHD on disease-associated and treatment-related mortality

We next evaluated the effects of acute GVHD on disease-associated and treatment-related mortality (Figure 1B-C). Disease-associated mortality was defined as cumulative incidence of death directly attributable to relapse or progression of ATL, whereas treatment-related mortality was calculated as cumulative incidence of any death not included in disease-associated deaths. Multivariate analysis revealed that disease-associated mortality was lower in the presence of grade 1-2 and grade 3-4 acute GVHD compared with the absence of acute GVHD (grade 1-2 acute GVHD: HR, 0.54; 95% CI, 0.32-0.92; $P = .023$ and grade 3-4 acute GVHD: HR, 0.44; 95% CI, 0.22-0.90; $P = .024$; Table 2), and each grade of acute GVHD showed consistent inverse association with disease-associated mortality (supplemental Table 1). Although the risk of treatment-related mortality was not higher in the presence of grade 1-2 acute GVHD, development of grade 3-4 acute GVHD was significantly associated with higher treatment-related mortality compared with the absence of acute GVHD (HR, 3.50; 95% CI, 2.01-6.11; $P < .001$; Table 2). Patients undergoing reduced intensity transplantation and those undergoing myeloablative transplantation had similar risks of disease-associated death (HR, 0.99; 95% CI, 0.46-2.13; $P = .975$) and treatment-related death (HR, 0.98; 95% CI, 0.60-1.59; $P = .928$) by multivariate analysis. There was no interaction effect between conditioning intensity and grade 1-2 or grade 3-4 acute GVHD on disease-associated mortality and treatment-related mortality. Of 95 patients who experienced treatment-related deaths, 27 patients succumbed to infectious complications: bacterial in 13 patients, viral in 7 patients (including 3 cases of cytomegalovirus disease), viral and bacterial in 1 patient, fungal in 5 patients, and no specific organism reported in 1 patient. The proportions of patients who died of infectious complication among those without acute GVHD (n = 92), those with grade 1-2 (n = 137), and those with grade 3-4 acute GVHD (n = 65) were 4%, 9%, and 17%, respectively (supplemental Table 3). By multivariate analysis, development of grade 3-4 acute GVHD was significantly associated with higher risk of death related to infection (HR, 4.74; 95% CI, 1.51-14.8; $P = .008$), whereas the adverse influence on the infection-related deaths was less evident in the presence of grade 1-2 acute GVHD (HR, 2.17; 95% CI, 0.72-6.56; $P = .169$).

Effects of chronic GVHD on overall survival and mortality

Chronic GVHD was evaluated in 183 patients who survived at least 100 days after transplantation. The median day of chronic GVHD occurrence after transplantation was 116 (range, 100-146 days). Limited and extensive chronic GVHD occurred in 29 (16%) and 63 patients (34%), respectively. Semi-landmark plots were constructed to illustrate the effects of chronic GVHD on overall survival, disease-associated mortality, and treatment-related mortality with reference to the following subgroups: no chronic GVHD, limited chronic GVHD, and extensive chronic GVHD (Figure 3). In multivariate analysis treating an occurrence of chronic GVHD as a time-dependent covariate, neither overall survival nor disease-associated mortality was significantly associated with severity of chronic GVHD, whereas treatment-related mortality was higher in the presence of extensive chronic GVHD (HR, 2.75; 95% CI, 1.34-5.63; $P = .006$) compared with the absence of chronic GVHD (Table 3). The proportions of patients who died of infectious complication among those without chronic GVHD (n = 91), those with limited chronic GVHD (n = 29), and those with extensive chronic GVHD (n = 63) were 7%, 10%, and 8%, respectively. In multivariate analysis, no statistically significant association was found between infection-related death and the occurrence of either limited ($P = .289$) or extensive GVHD ($P = .836$).

Discussion

To our knowledge, this is the largest retrospective study to analyze the impact of acute and chronic GVHD on clinical

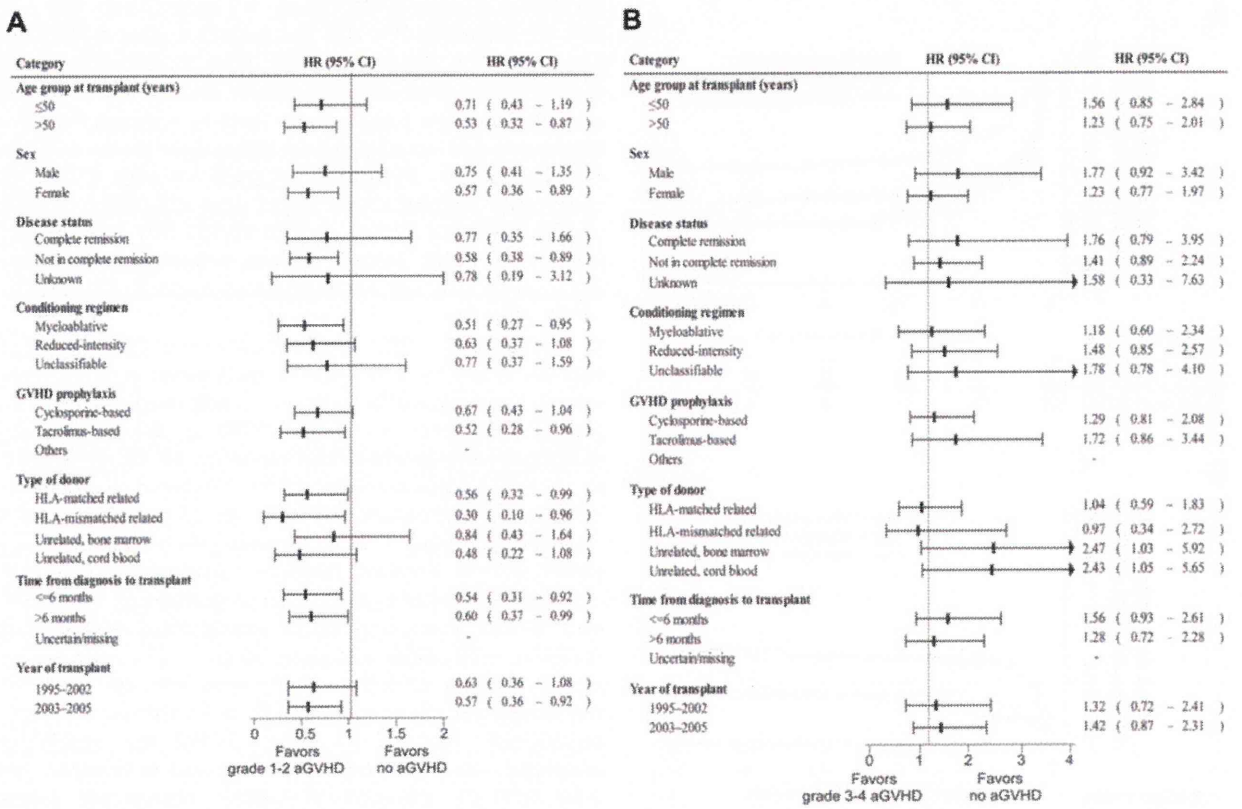

Figure 2. Impact of the grade of acute GVHD on overall survival in each stratified category. Effects of grade 1-2 (A) and grade 3-4 acute GVHD (B) on overall survival are shown as forest plots. Square boxes on lines indicate hazard ratios compared with "no acute GVHD group." and horizontal lines represent the corresponding 95% CI. Abbreviations used are the same as described in the footnotes to Tables 1 and 2.

outcomes including overall survival, disease-associated mortality, and treatment-related mortality after allogeneic HCT for ATL. In the present study, the occurrence of both grade 1-2 and grade 3-4 acute GVHD was associated with lower disease-associated mortality compared with the absence of acute GVHD. However, positive effect of GVHD on reduced disease-associated mortality was counterbalanced by increased treatment-related mortality among patients who developed severe acute GVHD, and an overall beneficial effect on survival was observed only with the development of mild-to-moderate acute GVHD. In contrast to acute GVHD, no beneficial effect was observed in association with the development of chronic GVHD, although the point estimate of the HR comparing limited chronic GVHD versus the absence of chronic GVHD

Table 2. Effect of acute GVHD on overall survival, disease-associated mortality, and treatment-related mortality after allogeneic hematopoietic cell transplantation for adult T-cell leukemia

	Univariate analysis		Multivariate analysis	
Outcome	HR (95% CI)	P	HR (95% CI)	P
Overall survival*				
Grade 1 or 2 acute GVHD vs no acute GVHD	0.60 (0.42-0.85)	.004	0.65 (0.45-0.93)	.018
Grade 3 or 4 acute GVHD vs no acute GVHD	1.38 (0.94-2.01)	.099	1.64 (1.10-2.42)	.014
Disease-associated mortality†				
Grade 1 or 2 acute GVHD vs no acute GVHD	0.47 (0.28-0.79)	.005	0.54 (0.32-0.92)	.023
Grade 3 or 4 acute GVHD vs no acute GVHD	0.41 (0.21-0.81)	.010	0.44 (0.22-0.90)	.024
Treatment-related mortality‡				
Grade 1 or 2 acute GVHD vs no acute GVHD	1.13 (0.67-1.89)	.649	1.22 (0.72-2.07)	.461
Grade 3 or 4 acute GVHD vs no acute GVHD	3.34 (1.94-5.74)	< .001	3.50 (2.01-6.11)	< .001

*Other significant variables were sex of recipient, female (reference, 1.00) and male (HR, 1.70; 95% CI, 1.24-2.32; $P = .001$); achievement of complete remission, complete remission (reference, 1.00), status other than complete remission (HR, 2.05; 95% CI, 1.44-2.92; $P < .001$), and status not known (HR, 2.21; 95% CI, 1.15-4.22; $P = .017$); type of donor, HLA-matched related donor (reference, 1.00), HLA-mismatched related donor (HR, 1.71; 95% CI, 1.04-2.84; $P = .036$), unrelated donor of bone marrow (HR, 1.39; 95% CI, 0.94-2.06; $P = .096$), and unrelated cord blood (HR, 1.86; 95% CI, 1.22-2.83; $P = .004$).

†Other significant variables were achievement of complete remission, complete remission (reference, 1.00), status other than complete remission (HR, 2.98; 95% CI, 1.62-5.47; $P < .001$), and status not known (HR, 0.96; 95% CI, 0.21-4.49; $P = .963$); type of donor, HLA-matched related donor (reference, 1.00), HLA-mismatched related donor (HR, 2.14; 95% CI, 1.00-4.55; $P = .049$), unrelated donor of bone marrow (HR, 1.45; 95% CI, 0.81-2.61; $P = .214$), and unrelated cord blood (HR, 1.25; 95% CI, 0.63-2.49; $P = .517$).

‡Another significant variable was achievement of complete remission, complete remission (reference, 1.00), status other than complete remission (HR, 1.17; 95% CI, 0.74-1.84; $P = .498$) and status not known (HR, 2.31; 95% CI, 1.04-5.15; $P = .040$).

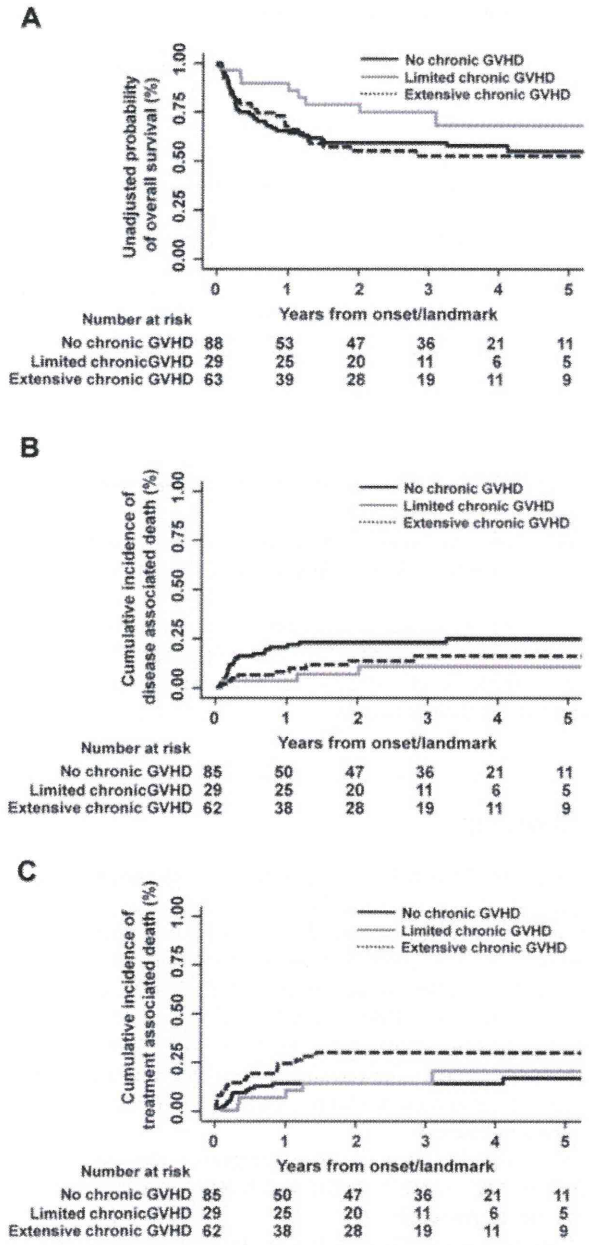

Figure 3. Semi-landmark plots for impact of chronic GVHD. Semi-landmark plots illustrating impact of chronic GVHD on overall survival (A), disease-associated mortality (B), and treatment-related mortality (C).

suggested the trend toward a reduced risk of disease-associated deaths in the limited chronic GVHD group.

Our present findings are in contrast to the previous reports showing the beneficial effects of chronic GVHD rather than acute GVHD on the prevention of disease recurrence after allogeneic HCT. It is less likely that the particular characteristics of chronic GVHD in patients with ATL biased the results, because the incidence rate and median onset day of chronic GVHD in our cohort were similar to those reported in previous studies evaluating the incidence of chronic GVHD among Japanese patients, most of whom had received allogeneic HCT for myeloid neoplasms or acute lymphoblastic leukemia.[30-32] Conceivably, the rapid tempo of disease recurrence of ATL might be such that chronic GVHD is less potent in terms of harnessing clinically relevant graft-versus-leukemia responses compared with acute GVHD. However, the results of our analysis regarding the effect of chronic GVHD should be interpreted with caution because the number of patients evaluable for chronic GVHD was relatively small in our study for providing sufficient statistical power. The effect of chronic GVHD on outcomes after HCT for ATL should be further explored in a larger cohort.

The occurrence of GVHD has been shown to exert a potent graft-versus-leukemia effect in terms of reducing relapse incidence in acute leukemia or chronic myeloid leukemia.[33,34] In contrast, multiple studies have documented a correlation between GVHD in its acute or chronic form and treatment-related mortality. In a study of patients undergoing HLA-identical sibling HCT for chronic myeloid leukemia, the overall beneficial effect on long-term survival was demonstrated only in a group of patients who developed grade 1 acute GVHD or limited chronic GVHD.[33] In another study of HLA-identical sibling HCT for leukemia using cyclosporine and methotrexate as GVHD prophylaxis, a benefit of mild GVHD was only seen in high-risk patients but not in standard-risk patients. Therefore, the therapeutic window between decreased relapse incidence and increased transplant-related mortality in association with the development of GVHD has been considered to be very narrow.[34]

With regard to the effectiveness of allogeneic HCT for ATL, it is also of note here that posttransplant eradication of ATL cells can be achieved without the use of high-dose chemoradiotherapy: patients who received a transplant with reduced intensity conditioning had survival outcomes similar to those who received a transplant with myeloablative conditioning in our study. Intriguingly, several small cohort studies exhibited that abrupt discontinuation of immunosuppressive agents resulted in disappearance or reduction in the tumor burden in allografted patients with ATL. In some cases, remission of ATL was observed along with the development of GVHD.[19,20,22] Taken together with the findings of this study, it is suggested that ATL is particularly susceptible to immune modulation following allogeneic HCT. To clarify the presence of such "graft-versus-ATL" effect, further investigations are needed to assess the efficacy of donor lymphocyte infusion or withdrawal of immunosuppressive agents on relapse after transplantation.

Of the HTLV-I gene products, Tax is a dominant target of HTLV-I–specific cytotoxic T lymphocytes. The vigorous Tax-specific cytotoxic T-cell responses were demonstrated in recipients who obtained complete remission after allogeneic HCT for ATL, suggesting that "graft-versus-HTLV-I" responses might contribute to the eradication of ATL cells.[35,36] However, Tax is generally undetectable or present in very low levels in primary ATL cells.[37,38] In addition, small amounts of HTLV-I provirus can be detected in peripheral blood of recipients who attained long-term remission of ATL, even after HCT from HTLV-I–negative donors.[39,40] These findings suggest that "graft-versus-ATL" effect can be harnessed without complete elimination of HTLV-I. It is also important to note that allogeneic HCT is emerging as an effective treatment option for other mature T-cell neoplasms not related to HTLV-I, such as mycosis fungoides/Sézary syndrome and various types of aggressive peripheral T-cell lymphomas.[41,42] These observations raised the possibility that the common targets for alloimmune responses might exist across a spectrum of malignant T-cell neoplasms, including ATL. The minor histocompatibility antigens or tumor-specific antigens can be other targets of alloimmune anti-ATL effect.[43-45] Therefore, the elucidation of the mechanism underlying an immunologic eradication of primary ATL cells may

Table 3. Effect of chronic GVHD on overall survival, disease-associated mortality, and treatment-related mortality after allogeneic hematopoietic cell transplantation for adult T-cell leukemia

Outcome	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Overall survival*				
Limited chronic GVHD vs no chronic GVHD	0.71 (0.34-1.47)	.353	0.72 (0.35-1.50)	.385
Extensive chronic GVHD vs no chronic GVHD	1.45 (0.90-2.35)	.131	1.40 (0.86-2.30)	.176
Disease-associated mortality†				
Limited chronic GVHD vs no chronic GVHD	0.45 (0.14-1.46)	.183	0.45 (0.14-1.44)	.178
Extensive chronic GVHD vs no chronic GVHD	0.81 (0.39-1.67)	.563	0.80 (0.39-1.64)	.536
Treatment-related mortality‡				
Limited chronic GVHD vs no chronic GVHD	1.59 (0.64-3.95)	.316	1.56 (0.63-3.87)	.342
Extensive chronic GVHD vs no chronic GVHD	2.85 (1.41-5.77)	.004	2.75 (1.34-5.63)	.006

*There was no significant variable.
†There was no significant variable.
‡There was no other significant variable.

lead to a new strategy for improving outcomes of allogeneic HCT not only for ATL but also for other intractable T-cell neoplasms.

This study has several limitations. First, acute GVHD might be intentionally induced for some patients considered at high risk of relapse by treating clinicians. Second, the information on the day when each grade of GVHD occurred was not available. Therefore, we treated the development of acute and chronic GVHD in their worst severity as a time-varying covariate. To validate the results, we also performed the landmark analysis and obtained consistent results. Third, the relatively small number of patients with chronic GVHD might mask or bias the effect of chronic GVHD on outcomes. Last, the effect of multiple testing should be taken into account for the interpretation of the secondary end points.

In conclusion, the development of acute GVHD was associated with lower disease-associated mortality after allogeneic HCT for ATL compared with the absence of acute GVHD. However, improved survival can be expected only among a group of patients who developed mild-to-moderate acute GVHD because those who developed severe acute GVHD were at high risk of treatment-related mortality. New strategies that enhance the allogeneic anti-ATL effect without exacerbating GVHD are required to improve the outcomes of patients undergoing allogeneic HCT for ATL.

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The views expressed in this report are those of authors and do not indicate the views of the JSHCT, JMDP, or JCBBN.

This work is in memory of T.U., who died during the preparation of this manuscript.

Authorship

Contribution: T.I. and T.U. designed the research and organized the project; M. Hishizawa, J.K., T.I., and T.U. reviewed and analyzed data and wrote the paper; J.K., T.I., and K.M. performed statistical analysis; Y.A., R.S., and H.S. collected data from JSHCT; T.K. and Y. Morishima collected data from JMDP; T.N.-I., and S. Kato collected data from JCBBN; and A.U., S.T., T.E., Y. Moriuchi, R.T., F.K., Y. Miyazaki, M.M., K.N., M. Hara, M.T., S. Kai, and J.O. interpreted data and reviewed and approved the final manuscript.

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A list of other members who contributed data on allogeneic HSCT for ATL to JSHCT, JMDP, and JCBBN appears in the online supplemental Appendix.

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