Ⅳ. 学会発表一覧

＜ 学会発表一覧 ＞

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
Kurosawa S, **Yamaguchi T**, Uchida N, Sakura S, Kanamori H, Usuki K, Yamashita T, Yatanabe M, Yakushiji K, Yano S, Nawa Y, Taguchi J, Takeuchi J, Takaue Y, **Fukuda T**.	Prognosis of Adult Patients with non-M3 AML after First Relapse	Biol Blood Marrow Transplant 16 (suppl2), 2010: ASBMT/IBMTR Tandem BMT Meetings, Orlando, USA (Oral presentation)	2010
Kurosawa S, **Yamaguchi T**, Uchida N, Miyawaki S, Kanamori H, Usuki K, Yamashita T, Watanabe M, Yakushiji K, Yano S, Nawa Y, Miura I, Kanda Y, Takaue Y, **Fukuda T**.	A Markov Decision Analysis of Post-Remission Strategies in 2029 Patients with AML in First Remission (CR1)	Biol Blood Marrow Transplant 16 (suppl2), 2010: ASBMT/IBMTR Tandem BMT Meetings, Orlando, USA (Oral presentation)	2010
Ueno N, Fuji S, **Fukuda T**, Yakushijin K, Kurosawa S, Asakura Y, Mori M, Hiramoto N, Kamiyama Y, Fukuhara S, **Kim SW**, Mori S, Tanosaki R, Heike Y, Takaue Y.	Low-Dose Anti-T-Lymphocyte Globulin (ATG-Fresenius) Significantly Reduces Acute GVHD and Non-Relapse Mortality (NRM) after Reduced-Intensity Unrelated BMT.	Biol Blood Marrow Transplant 16 (suppl2), 2010: ASBMT/IBMTR Tandem BMT Meetings, Orlando, USA (Poster presentation)	2010
Yakushijin K, **Fukuda T**, Asakura Y, Kurosawa S, Hiramoto N, Tada K, Nishinohara M, Maeda T, Hagiwara A, Ueno N, Kamiyama Y, Mori M, **Kim SW**, Mori S, Tanosaki R, Heike Y, Takaue Y.	Cladribine (2CdA) Is Comparable to Fludarabine in a Busulfan-Based Reduced-Intensity Regimen.	Biol Blood Marrow Transplant 16 (suppl2), 2010: ASBMT/IBMTR Tandem BMT Meetings, Orlando, USA (Poster presentation)	2010
Kurosawa S, **Yamaguchi T**, Miyawaki S, Uchida N, Kanamori H, Yamashita T, Usuki K, Watanabe M, Yakushiji K, Yano S, Nawa Y, Taguchi J, Takeuchi J, Nakamura Y, Tomiyama J, Nannya Y, Okoshi Y, Sano F, Shibayama H, Hino M, Moriuchi Y, **Kanda Y**, **Fukuda T**.	Comparison of allogeneic hematopoietic cell transplantation and chemotherapy in adult patients with non-M3 AML staying in CR1: A retrospective nation-wide survey	The 35th Annual Meeting of the European Group for Blood and Marrow Transplantation, Göteborg, Sweden (Oral presentation)	2009
Yakushijin K, **Fukuda T**, Asakura Y, Kurosawa S, Hiramoto N, Nakamura D, Tada K, Nishinohara M, Hagiwara A, Ueno N, Kamiyama Y, Mori M, **Kim SW**, Mori SI, Tanosaki R, Heike Y, Takaue Y.	Renal Complications after Busulfan-Based Reduced-Intensity Stem Cell Transplantation in 286 Patients with Hematological Disorders.	The 51th Annual Meeting of the American Society of Hematology, New Orleans, USA (Poster presentation)	2009
平本展大, **福田隆浩**, 黒澤彩子, 薬師神公和, 朝倉義崇, 神山祐太郎, 上野二菜, 西之原正昭, **金 成元**, 森 慎一郎, 田野崎隆二, 平家勇司, 高上洋一.	当院における骨髄異形成症候群（MDS）に対する同種造血幹細胞移植（allo-HCT）の検討（WS2-10-5）	第32回日本造血細胞移植学会総会（浜松）	2010

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
上野二菜, 福田隆浩	非血縁骨髄ミニ移植：単施設における108件の検討	第32回日本造血細胞移植学会総会（浜松）	2010
臼杵憲祐, 黒澤彩子, 福田隆浩	第一寛解期急性骨髄性白血病に対する自家移植	第32回日本造血細胞移植学会総会（浜松）	2010
黒澤彩子, 山口　拓洋, 福田隆浩	第一寛解期急性骨髄性白血病に関するマルコフモデルを用いた臨床決断分析	第32回日本造血細胞移植学会総会（浜松）	2010
薬師神公和, 福田隆浩	骨髄非破壊的前処置による造血幹細胞移植(RIST) 286例における腎障害の後方視的検討	第32回日本造血細胞移植学会総会（浜松）	2010
西之原正昭, 福田隆浩	生着不全に対する臍帯血移植・血縁ハプロ適合移植	第32回日本造血細胞移植学会総会（浜松）	2010
黒澤彩子, 山口　拓洋, 福田隆浩	第一再発急性骨髄性白血病の予後とリスク因子に関する検討	第32回日本造血細胞移植学会総会（浜松）	2010
佐倉 徹, 黒澤彩子, 福田隆浩	第一寛解期急性前骨髄球性白血病の予後	第32回日本造血細胞移植学会総会（浜松）	2010
黒澤彩子, 山口　拓洋, 福田隆浩	中間リスク急性骨髄性白血病第一寛解期の臨床決断分析：多施設共同研究（シンポジウム）	第71回日本血液学会学術集会（京都）	2009
Kurosawa S, **Yamaguchi T**, Uchida N, Miyawaki S, Usuki K, Watanabe M, Yamashita T, Kanamori H, Tomiyama J, Nawa Y, Yano S, Takeuchi J, Yakushiji K, Sano F, Uoshima N, Yano T, Nannya Y, Moriuchi Y, Taguchi J, Okoshi Y, Tohmiya Y, Takaue Y, **Fukuda T**.	Nation-wide survey of elderly patients with AML in CR1（口演）	第71回日本血液学会学術集会（京都）	2009

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
岡村篤夫、松井利充　他13名	急性GVHD予防薬ミコフェノール酸モチフェル(MMF)至適投与法の確立に関する研究(第4報)	第32回日本造血細胞移植学会総会（浜松）	2010
井上潤一郎、松井利充　他8名	同種造血幹細胞移植患者の運動イメージはリハビリテーションにより改善するか？	第32回日本造血細胞移植学会総会（浜松）	2010
高見昭良	IL-17A遺伝子多型はHLA一致非血縁者間骨髄移植成績に影響する	第71回日本血液学会学術集会（京都）	2009
Takami A.	Significant Impact of IL-17A Gene Polymorphism On Transplant Outcomes After HLA-Fully-Matched Unrelated Bone Marrow Transplantation.	The 51th Annual Meeting of the American Society of Hematology (New Orleans, USA)	2009
Takami A.	A single nucleotide polymorphism of the Fcgamma receptor type IIIA gene in the recipient predicts transplant outcomes after HLA-fully-matched unrelated bone marrow transplantation for myeloid malignancies.	The 36th Annual Meeting of the European Group for Blood and Marrow Transplantation (Vienna, Austria)	2010
Kodera Y, Kim S, Nagafuji K, Hino M, Miyamura K, **Suzuki R**. for the Japan Society for Hematopoietic Cell Transplantation.	Preregistration and five-year follow-up system for bone marrow and peripheral blood stem cell family donors: the interim report.	The 35th Annual Meeting of the European Group for Blood and Marrow Transplantation (Oral presentation) (Goteborg, Sweden)	2009
Kodera Y, Iida M, Atsuta Y, Yoshimi A, **Suzuki R**.	Current status, history and future prospects of blood and marrow transplantation in Japan, and the progress of WBMT since the last February.	The 14th Congress of the Asia-Pacific Blood and Marrow Transplantation Group 2009 (Oral presentation) (Seoul, Korea)	2009
Suzuki R, Terakura S, Kohno A, Sawa M, Kuwatsuka Y, Atsuta Y, Murata M, Miyamura K, Fukumoto M, Morishita Y.	Individual dose adjustment of oral busulfan in conditioning regimen coupled with cyclophosphamide.	The 14th Congress of the Asia-Pacific Blood and Marrow Transplantation Group 2009 (Poster) (Seoul, Korea)	2009
Iida M, **Suzuki R**, Atsuta Y, Min C-K, Wu T Nivison-Smith I, Khatami F, Bihn TV, Lie A, Chan LL, Jootar S, Hwang W, Srivastava A, Tesneem F, Kodera Y.	Activity survey of hematopoietic stem cell transplantation (HSCT) in the Asia-Pacific Blood and Marrow Transplantation Group (APBMT).	The 14th Congress of the Asia-Pacific Blood and Marrow Transplantation Group 2009 (Poster) (Seoul, Korea)	2009
Suzuki R, Yamaguchi M, Izutsu K, Yamamoto G, Takada K, Harabuchi Y, Isobe Y, Gomyo H, Koike T, Okamoto M, Suzumiya J, Nakamura S, Kawa K, Oshimi K.	Prospective measurement of EBV-DNA in plasma and peripheral blood mononuclear cells of extranodal NK/T-cell lymphoma, nasal type.	The 51th Annual Meeting of the American Society of Hematology (Oral presentation, Abstract #135) (New Orleans, USA)	2009

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
Terakura S, Sawa M, Ohashi H, Kato T, Nishiwaki S, Imahashi N, Murata M, Miyamura K, Atsuta Y, **Suzuki R**, Naoe T, Ito T, Morishita Y.	Optimization of fludarabine + melphalan conditioning for marrow transplantation from unrelated donors for patients with hematopoietic malignancies: a prospective dose-finding trial using modified continual reassessment method.	The 51th Annual Meeting of the American Society of Hematology (Poster, Abstract #2273) (New Orleans, USA)	2009
Shigematsu A, Tanaka J, **Suzuki R**, Kawase T, Akiyama H, Fukuda T, Kumano K, Yoshiba F, Kanamori H, Kobayashi N, Fukuhara T, Imamura M.	Superior outcomes using medium-dose VP-16/CY/TBI to CY/TBI as a conditioning regimen for allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia.	The 51th Annual Meeting of the American Society of Hematology (Poster, Abstract #2306) (New Orleans, USA)	2009
澤 正史、福本真理子、寺倉精太郎、鍬塚八千代、安田貴彦、稲本賢弘、宮村耕一、齊藤繁紀、島田和之、河野彰夫、村田　誠、烏野隆博、谷口修一、長藤宏司、熱田由子、**鈴木律朗**、森下剛久	用量調節経口ブスルファンとシクロフォスファミドを用いた造血幹細胞移植におけるブスルファン血中濃度解析	第71回日本血液学会学術集会（京都）	2009
熱田由子、**鈴木律朗**、山下卓也、**福田隆浩**、宮村耕一、坂巻 壽、小寺良尚	成人血縁者間造血幹細胞移植における二次性固形腫瘍	第71回日本血液学会学術集会（京都）	2009
Kadowaki M, Sakoda Y, Takashima S, Aoyama K, Koyama M, Hashimoto D, Akashi K, **Teshima T**.	Depletion of regulatory T cells causes chronic GVHD in experimental bone marrow transplantation.	第71回日本血液学会学術集会（京都）	2009
Aoki T, Miyamoto T, Yoshida S, Yamamoto A, Kamezaki K, Iwasaki H, Takenaka K, Harada N, **Teshima T**, Akashi K.	Additional acquisition of t(1;21) in a patient relapsing with AML with NUP98-HOXA9.	第71回日本血液学会学術集会（京都）	2009
Mori Y, Yamauchi T, Miyamoto T, Aoki T, Yamamoto A, Kamezaki K, Takenaka K, Iwasaki H, Harada N, Nagafuji K, **Teshima T**, Akashi K.	Reduced intensity cord blood transplantation with GO for relapsed AML patients.	第71回日本血液学会学術集会（京都）	2009
Takashima S, Asakura S, Hashimoto D, Tanimoto M, Akashi K, **Teshima T**.	Activation of PD-1/PD-L1 interaction by graft-versus-host disease paradoxically impairs GVL effects.	第71回日本血液学会学術集会（京都）	2009

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
高嶋秀一郎，門脇賢典、青山一利，小山幹子，大島毅、富塚一磨、赤司浩一，原田実根，豊嶋崇徳	R-spondin1 は移植前処置から腸管を保護し、移植片対宿主病(GVHD)を改善する	第32回日本造血細胞移植学会総会（浜松）	2010
飯田美奈子、福田隆浩、池亀和博、吉原 哲、小川啓恭、谷口修一、高見昭良、安部康信、日野雅之、衛藤徹也、熱田由子、田中淳司、鈴木律朗	我が国における血縁同種造血幹細胞移植での Mycophenolate Mofetil（MMF）使用全国実態調査結果報告	第71回日本血液学会学術集会（京都）	2009
林 良樹、中根孝彦、中前博久、康 秀男、中前美佳、西本光孝、吉村卓朗、井上恵里、井上敦司、相本 蘭、相本瑞樹、寺田芳樹、高 起良、山根孝久、日野雅之	Ara-C+CY+TBI を前処置とした非血縁臍帯血移植の予後因子の当科での検討	第32回日本造血細胞移植学会総会（浜松）	2010
中根孝彦、中前博久、康 秀男、中前美佳、林 良樹、西本光孝、吉村卓朗、井上恵里、井上敦司、相本 蘭、相本瑞樹、寺田芳樹、高 起良、山根孝久、日野雅之	シクロスポリン（CsA）＋短期メソトレキセート（sMTX）をGVHD予防とした非T細胞除去・非TBI下での骨髄非破壊的非血縁者間同種骨髄移植（u-RIST）の検討	第32回日本造血細胞移植学会総会（浜松）	2010
望月朋美、萩原將太郎	造血幹細胞移植患者の長期フォローアップ外来の試み	第32回日本造血細胞移植学会総会（浜松）	2010
Takahashi S, Ishige M, Watanabe N, **Yamaguchi T**, et al.	Prospective analysis for antigen-specific cellular immune reconstitution after cord blood transplantation: Immune response to CMV is not affected by HLA disparity.	The 35th Annual Meeting of the European Group for Blood and Marrow Transplantation (Goteborg, Sweden)	2009
Kurosawa S, **Yamaguchi T**, Uchida N, Miyawaki S, Kanamori H, Usuki K, Yamashita T, Watanabe M, Yakushiji Y, Yano S, Nawa Y, Taguchi J, Takeuchi J, Nakamura Y, Nannya Y, Okoshi Y, **Kanda Y**, Miura I, Takaue Y, **Fukuda T**.	A Markov Decision Analysis of Post-Remission Strategies in 2029 Patients with AML in First Remission (CR1): Should We Perform Allogeneic Hematopoietic Cell Transplantation in CR1?	Blood (ASH Annual Meeting Abstracts) 114: 2281	2009
Kurosawa S, **Yamaguchi T**, Uchida N, Sakura T, Usuki K, Watanabe M, Yamashita T, Kanamori H, Tomiyama J, Nawa Y, Yano S, Takeuchi J, Yakushiji K, Sano F, Uoshima N, Nannya Y, Moriuchi Y, Takaue Y, **Fukuda T**.	Comparison of Allogeneic Hematopoietic Cell Transplantation and Chemotherapy as Post-Remission Strategy in Elderly Patients with Non-M3 AML in CR1: Retrospective Analysis with 1036 Patients.	Blood (ASH Annual Meeting Abstracts) 114: 524	2009

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
Takahashi S, Ooi J, Tsukada N, Kato S, Sato A, Kawakita T, Nagata Y, Monna-Ooiwa M, Tojo S, **Yamaguchi T**, Morishima S, Morishima Y, Asano S.	The Impact of HLA Haplotype Matching for Mismatched Cord Blood Transplantation.	Blood (ASH Annual Meeting Abstracts) 114: 1206	2009
Mori T, kato J, Aisa Y, Yamane A, Ono Y, Okamoto S.	Drug interaction between oral calcineurin inhibitors (tacrolimus and cyclosporine A) and oral voriconazole in the recipients of allogeneic haematopoietic stem cell transplantation.	Biol Blood Marrow Transplant 16(suppl2):S260 (ASBMT/IBMTR Tandem BMT Meetings, Orlando, poster)	2010
森 毅彦、相佐好伸、加藤淳、池田康夫、岡本真一郎	同種造血幹細胞移植患者における経口 voriconazole と経口 tacrolimus/CsA の薬物相互作用の検討　（口演）	第 71 回日本血液学会学術集会（京都）	2009
Kim SW, Yoon SS, **Suzuki R**, Yi HG, Ago H, Imamura M, Wake A, Yoshida T, Lee JJ, Kim JS, Maeda Y, Izutsu K, Kang HJ, Lee JH, Kim HC, Suzumiya J, Matsuno Y, Kim CW, Nagafuji K, Takaue Y, Harada M, Kim CS.	Autologous Versus Allogeneic Hematopoietic Stem Cell Transplantation (SCT) for Peripheral T-cell Lymphomas (PTCLs): Japan and Korea Cooperative Study with 330 Patients.	Blood (ASH Annual Meeting Abstracts) 114: 901	2009
Tanosaki R, Yakushijin K, Asakura Y, Kurosawa S, Hiramoto N, Mori M, **Fukuda T**, **Kim SW**, Mori SI, Heike Y, Tobinai K, Takaue Y.	Long-Term Outcome of ATL Patients Who Underwent Reduced-Intensity Stem Cell Transplantation (RIST): Suggested Potent Graft-Versus-ATL and HTLV-1 Effects.	Blood (ASH Annual Meeting Abstracts) 114: 1308	2009
Kamiyama Y, Makimoto A, **Kim SW**, Yakushijin K, Hosono A, Ueno N, Fukuhara S, Hiramoto N, Asakura Y, Kurosawa S, **Fukuda T**, Mori S, Tanosaki R, Heike Y, Takaue Y.	Allogeneic Hematopoietic Stem Cell Transplantation with a Reduced-Intensity Conditioning Regimen (RIST) for the Treatment of Solid Tumors: A Single-Institute Experience.	Biology of Blood and Marrow Transplantation (BMT Tandem Meetings) 16: 261	2010
Kim SW, Fuji S, **Fukuda T**, Mori S, Kamiya S, Furuta K, Yokoyama H, Kurosawa S, Saito B, Kuwahara S, Heike Y, Tanosaki R, Takaue Y.	Elevated Serum Leptin Level in Patients with Persistent Anorexia after Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT).	Biology of Blood and Marrow Transplantation (BMT Tandem Meetings) 16: 272	2010
Kim SW.	Comparison of Transplant Outcomes Focusing on GVHD between Two Neighboring Countries. KSBMT/JSHCT Joint Symposium.	第 32 回日本造血細胞移植学会総会（浜松）	2010

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
渡部大介, 小井土啓一, 文 靖子, 宇田川涼子, 横手信昭, 金成元, 福田隆浩, 森 慎一郎, 田野崎隆二, 高上洋一, 山本弘史.	造血幹細胞移植後の tacrolimus 持続静注クリアランスは経口投与量決定のための要因になるかもしれない（PS1-73）	第32回日本造血細胞移植学会総会（浜松）	2010

Ⅴ．研究成果の刊行物（論文別刷）

Outcome of 93 patients with relapse or progression following allogeneic hematopoietic cell transplantation

Saiko Kurosawa, Takahiro Fukuda,* Kinuko Tajima, Bungo Saito, Shigeo Fuji, Hiroki Yokoyama, Sung-Won Kim, Shin-Ichiro Mori, Ryuji Tanosaki, Yuji Heike, and Yoichi Takaue

Relapse/progression after allogeneic hematopoietic cell transplantation (allo-HCT) remains the major cause of treatment failure. In this study, the subsequent clinical outcome was overviewed in 292 patients with leukemia/myelodysplastic syndrome who received allo-HCT. Among them, 93 (32%) showed relapse/progression. Cohort 1 was chosen to receive no interventions with curative intent (n = 25). Cohort 2 received reinduction chemotherapy and/or donor lymphocyte infusion (n = 48), and Cohort 3 underwent a second allo-HCT (n = 20). Sixty-three patients received reinduction chemotherapy, and 27 (43%) achieved subsequent complete remission (CR). The incidence of nonrelapse mortality (NRM) was similar among the three cohorts (4, 15, and 5%). The 1-year overall survival (OS) after relapse was significantly better in patients with a second HCT (58%) than in others (14%, Cohorts 1 and 2; P < .001). However, the 2-year OS did not differ between the two groups, which suggests that it is difficult to maintain CR after the second HCT. Multivariate analysis showed that reinduction chemotherapy, CR after intervention, second HCT, and longer time to post-transplant relapse were associated with improved survival. In conclusion, for patients with relapse after allo-HCT, successful reinduction chemotherapy and a second HCT may be effective for prolonging survival without excessive NRM. However, effective measures to prevent disease progression after a second HCT clearly need to be developed. Am. J. Hematol. 84:815–820, 2009. © 2009 Wiley-Liss, Inc.

Introduction

Relapse or progression of leukemia occurring after allogeneic hematopoietic cell transplantation (allo-HCT) remains the major cause of post-transplantation mortality, with a median postrelapse survival of 1.6–6 months when aggressive intervention is suspended [1–6]. The optimal treatment strategy for these patients has not yet been established. Although some patients can be reinduced into complete remission (CR) with conventional chemotherapy, only a few become long-term survivors while maintaining conventional chemotherapy [4–6], and the benefit of donor lymphocyte infusion (DLI) for acute leukemia is limited [1,3,7].

Several studies have shown that a second allo-HCT improved survival after relapse and represents a potential therapeutic option, which may increase the duration of leukemia-free survival (6–25 months) [1,6,8–14]. However, this is associated with a high rate of nonrelapse mortality (NRM) (24–75%) [8–13,15]. In many studies, the results regarding a second HCT are generally represented by heterogeneous cohorts of patients or series with relatively few patients carrying variable backgrounds. Furthermore, most studies have not compared the outcome of a second HCT with that of other interventions in the modern treatment era.

To identify the factors that influence the outcome of patients with relapse after various salvage therapies, including second HCT, we performed a retrospective single-center analysis of consecutive 292 patients.

Patients and Methods

Patients. Between January 2000 and December 2006, a total of 292 patients with leukemia or myelodysplastic syndrome (MDS) underwent allo-HCT at the National Cancer Center Hospital. Recipients of haploidentical transplants from related donors and patients aged 15 or under were not included in this study. The characteristics of the patients and transplantations are summarized in Table I. The underlying diseases were AML (n = 142), MDS (n = 73), CML (n = 34), and ALL (n = 43). The median age at the initial HCT was 50 years (range: 16–68). Of the 292 patients, 148 received an initial HCT with myeloablative conditioning (cyclophosphamide plus fractionated TBI or busulfan), and the remaining 144 received reduced-intensity conditioning (RIC; fludarabine- or cladribine-based).

Definitions. Relapse/progression after transplantation was defined as the presence of or increase in leukemic blasts as detected by morphology either in bone marrow or peripheral blood. Detection of minimal residual disease by flow cytometry, PCR, or decreasing donor chimerism did not constitute evidence of recurrence in the absence of morphological abnormalities. CR was defined as normocellular bone marrow with less than 5% blasts along with the absence of blasts in the peripheral blood [16]. Postrelapse overall survival (OS) was measured from the date of relapse or progression to the time of death or censored date of last contact. Withdrawal of immunosuppression (WIS) was defined as the cessation of immunosuppression at the diagnosis of relapse or progression. Chemotherapy was categorized into two groups: reinduction chemotherapy and less-intensive chemotherapy intended for palliative treatment. Disease-specific reinduction chemotherapy included high-dose cytarabine, idarubicin + cytarabine, aclarubicin + low-dose cytarabine [17,18], and other remission-induction therapies for myeloid and lymphoid leukemia. Imatinib mesylate for CML, all-trans retinoic acid or arsenic trioxide for acute promyelocytic leukemia (APL), gemtuzumab ozogamicin for CD33-positive AML, and intrathecal chemotherapy alone for isolated central nervous system (CNS) relapse were also included in the reinduction chemotherapy group. Less-intensive chemotherapy included oral hydroxyurea, cytarabine or 6-mercaptopurine, and the sole intravenous administration of aclarubicin or vincristine, which are not thought to be intensive enough to achieve remission, but are aimed at palliation. NRM was defined as death from toxicities related to therapy without disease recurrence.

Interventions were categorized into three cohorts: Cohort 1, WIS or less-aggressive chemotherapy; Cohort 2, reinduction chemotherapy and/or DLI; Cohort 3, second allo-HCT.

Statistical analysis. Data were retrospectively reviewed and analyzed as of August 2007. The primary endpoint of the study was OS following relapse/progression. OS was estimated by the Kaplan-Meier method.

Department of Stem Cell Transplantation, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

Conflict of interest: Nothing to report.

*Correspondence to: Takahiro Fukuda, Department of Stem Cell Transplantation, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: tafukuda@ncc.go.jp

Received for publication 26 June 2009; Revised 17 September 2009; Accepted 30 September 2009

Am. J. Hematol. 84:815–820, 2009.

Published online 8 October 2009 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21555

The log-rank test and generalized Wilcoxon test were used to compare the probabilities of survival over time across patient subgroups. Multiple cox regression models were used for multivariate risk-factor analysis for OS following relapse/progression. The clinical factors evaluated were diagnosis, patient age at the initial HCT, gender, conditioning in the initial HCT (myeloablative or RIC), donor in the initial HCT (HLA-matched related or others), disease status at the initial HCT, interval from the initial HCT to relapse/progression, interventions that were chosen after relapse (Cohorts 1–3), and the response to the initial intervention. We considered two-sided *P*-values of <0.05 to be statistically significant. Statistical analyses were performed with the SPSS statistics and SAS version 8.2 (SAS, Cary, NC).

TABLE I. Patient and Transplanation Characteristics

Characteristics	All patients	Relapsed patients %[a]
No. of patients	292	93 (32)
Age, year, median (range)	50 (16–68)	47 (16–68)
Diagnosis[b]		
AML	142	57 (40)
MDS	73	13 (9)
CML	34	5 (4)
ALL	43	18 (13)
Gender		
Male	173	49 (35)
Female	119	44 (31)
Matched related donor		
Yes	125	44 (31)
No	167	49 (35)
Conditioning regimen		
Myeloablative		
TBI-based	90	38 (27)
BU/CY-based	58	21 (15)
RIC	144	34 (24)
Stem cell source		
BM	125	37 (26)
PBSC	149	49 (35)
CB	18	7 (5)
Disease status at first HCT		
CR	150	42 (30)
non-CR	142	51 (36)
GVHD prophylaxis		
CSP-based	243	77 (54)
TAC-based	49	16 (11)

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ALL, acute lymphoid leukemia; TBI, total body irradiation; BU/CY, busulfan/cyclophosphamide; RIC, reduced-intensity conditioning; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; CR, complete remission; GVHD, graft-versus-host disease; CSP, cyclosporin; TAC, tacrolimus.

[a] The percentage shown here indicates the proportion fo relapsed patients among each category.

[b] MDS overt leukemia was categorized into AML.

Results

Relapse or progression

The characteristics of all patients and relapsed patients are shown in Table I. Overall, 93 of the 292 patients (32%) relapsed or progressed at a median of 154 days (range; 15–1,211) after the initial HCT (AML, $n = 57$; MDS, $n = 13$; CML, $n = 5$; ALL, $n = 18$). The interval from the initial HCT to relapse/progression was less than 100 days in 34 patients, 100 days to 1 year in 39 patients, and more than 1 year in 20 patients.

TABLE II. Outcomes of Interventions after Relapse

Therapy	*n*	CR (%)	NRM (%)	OS after relapse, day, median, (range)
Total	93	34 (37)	9 (10)	184 (5–1456)
No aggressive Tx	25	1 (4)	1 (4)	61 (5–245)
No therapy	7	0	0	56 (22–166)
WIS alone	10	1	1	60 (5–245)
Less- int. CTx	8	0	0	74 (12–203)
Chemotherapy/DLI	48	18 (38)	7 (15)	194 (19–1,456)
Reinduction CTx	31	9 (29)	2 (6)	167 (19–1,456)
CTx + DLI	14	7 (50)	4 (29)	194 (52–1,254)
DLI alone	3	2 (67)	1 (33)	240 (32–243)
second HCT	20	15 (75)	1 (5)	502 (66–997)

CR, complete remission; NRM, nonrelapse mortality; OS, overall survival; Tx, therapy; WIS, withdrawal of immunosuppression; Less-int. CTx, less-intensive chemotherapy; DLI, donor lymphocyte infusion; HCT, hematopoietic cell transplantation.

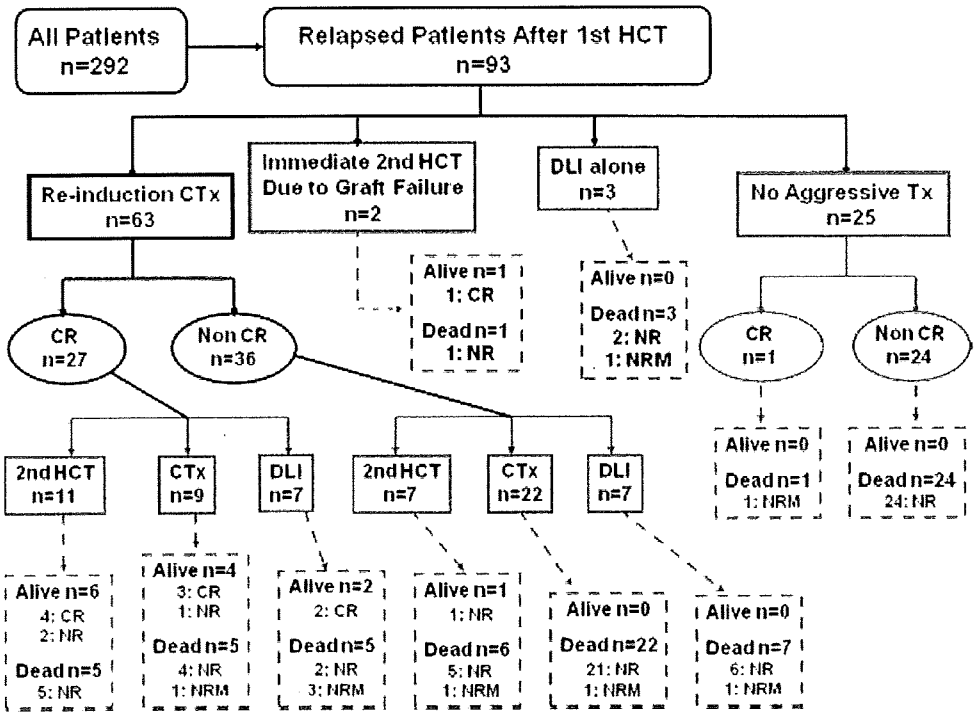

Figure 1. Summary of interventions after relapse. Abbreviations: HCT, hematopoietic cell transplantation; CTx, chemotherapy; Tx, therapy; CR, complete remission; DLI, donor lymphocyte infusion; NR, nonremission; NRM, nonrelapse mortality. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE III. Patient Characteristics of Intervention Group

Characteristics	No aggressive Tx (%)	CTx and/or DLI (%)	Second HCT (%)	*P*
Total no. of patients	25	48	20	
Diagnosis				0.053
AML	10 (40)	32 (67)	15 (75)	
MDS	7 (28)	3 (6)	3 (15)	
CML	2 (8)	3 (6)	0 (0)	
ALL	6 (24)	10 (21)	2 (10)	
Age				0.333
<50	11 (44)	28 (58)	13 (65)	
≥50	14 (56)	20 (42)	7 (35)	
Matched related donor				0.143
Yes	8 (32)	27 (56)	9 (45)	
No	17 (68)	21 (44)	11 (55)	
Disease status at first HCT				0.105
CR	7 (28)	26 (54)	9 (45)	
non-CR	18 (72)	22 (46)	11 (55)	
Time from first HCT to relapse				0.938
≥100 days	16 (64)	31 (65)	12 (60)	
<100 days	9 (36)	17 (35)	8 (40)	

Tx, therapy; CTx, chemotherapy; HCT, hematopoietic cell transplantation; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ALL, acute lymphoid leukemia; CR, complete remission.

Interventions after relapse/progression

After the diagnosis of relapse or progression, the need for salvage therapy was determined at a multiprofessional conference, at which the clinical circumstances and the opinions of physicians and patients were weighed. The various therapeutic options used after the diagnosis of relapse are summarized in Table II and Fig. 1.

At the diagnosis of relapse or progression, 70 patients had been receiving immunosuppression (median days after initial HCT, 125; range 15–705) and 63 of them had it withdrawn before receiving any other therapies.

After the diagnosis of relapse or progression, 63 patients received reinduction chemotherapy with disease-specific regimens, which included imatinib mesylate (CML, $n = 4$), all trans-retinoic acid and arsenic trioxide (APL, $n = 1$), gemtuzumab ozogamicin (AML, $n = 3$), and intrathecal chemotherapy alone for isolated CNS relapse (AML, $n = 3$; ALL, $n = 1$; CML, $n = 1$). Overall, 27 of the 63 patients who received reinduction chemotherapy achieved CR (43%). Among the 27 patients who achieved CR, 18 proceeded to DLI ($n = 7$) or second HCT ($n = 11$). The remaining nine received no further therapy other than chemotherapy; three patients with CNS relapse were in remission, and the remaining six patients subsequently progressed. Among the 36 patients who did not achieve CR, 14 proceeded to DLI ($n = 7$) or second HCT ($n = 7$), and the remaining 22 did not receive further treatment because of various reasons (disease progression, $n = 15$; infection and/or graft-versus-host disease (GVHD), $n = 4$; refusal, $n = 3$). Two other patients proceeded to second HCT directly after disease relapse with concomitant graft failure.

To compare the outcomes of the interventions after relapse/progression, we divided the 93 patients into three cohorts according to the intervention, that is, no aggressive therapy (Cohort 1, $n = 25$), reinduction chemotherapy and/or DLI without second HCT (Cohort 2, $n = 48$), and second HCT (Cohort 3, $n = 20$). There were no significant differences among the three groups in clinical characteristics such as patient age at the initial HCT, diagnosis, donor in the initial HCT, disease status at the initial HCT, and interval from the initial HCT to relapse (Table III).

No aggressive therapy (Cohort 1)

Among the 93 patients who relapsed, 25 (27%) received no aggressive therapy with curative intent other than WIS or less-intensive chemotherapy, mostly because of comorbidities and/or refractoriness of leukemia/MDS. Among the 10 patients who received WIS alone, only one achieved CR, but this patient subsequently died of bronchiolitis obliterans. All of the remaining eight patients who were given less-intensive chemotherapy alone and seven who received no therapy after relapse/progression died of disease progression without achieving CR. The median OS of the patients in Cohort 1 was 61 days after relapse/progression and the cause of death was primarily disease progression.

Reinduction chemotherapy and/or DLI without second HCT (Cohort 2)

Of the 63 patients who received reinduction chemotherapy after relapse, 45 patients did not receive a second HCT; these 45 patients with or without subsequent DLI and three other patients who received DLI without preceding chemotherapy were placed in Cohort 2.

Overall, 16 (36%) of the 45 patients achieved CR as the best response after reinduction chemotherapy. All three patients with isolated CNS relapse were alive in remission, whereas 11 of 13 patients who had marrow relapse eventually relapsed.

After reinduction chemotherapy, 14 patients (AML, $n = 9$; MDS, $n = 1$; ALL, $n = 3$; CML, $n = 1$) received DLI from the same donor as in the initial HCT. The initial CD3-positive cell dose of DLI ranged from 0.03 to 161 $\times$ 10^8/kg (median: 2.9 $\times$ 10^8/kg), and the number of courses of DLI was one to four, which were chosen according to the donor source or the disease status of patients at the discretion of physicians. Although the remission rate of patients who received DLI after chemotherapy was 50%, the incidence of NRM was also rather high (29%, GVHD with or without infection). The median OS of patients who received DLI after relapse/progression was 194 days (range: 52–1,254), which was similar to that of patients without DLI (167 days, range; 19–1,456).

Among the three patients who received DLI without preceding chemotherapy (AML, 1; MDS, 2), two achieved CR but all of them eventually died: one with toxicity and two with disease progression.

Second HCT (Cohort 3)

Table IV summarizes the profiles of 20 patients who underwent a second HCT. The median age at the initial HCT was 38 years (21–66 years) and 65% of the patients were younger than 50 years. The median time from the initial HCT to relapse/progression was 152 days (range: 21–1,211), and the median interval between the initial HCT and the second HCT was 325 days (range: 126–1,310). Six patients received HCT from the same donor as in the initial HCT (HLA-matched related donor, $n = 5$; unrelated bone marrow donor, $n = 1$), and the remaining 14 received the second HCT from a different donor (unrelated bone marrow donor, $n = 7$; cord blood, $n = 6$; haploidentical related do-

TABLE IV. Characteristics of Second Transplantation

Characteristics	No of patients second HCT (%)
Total	20
Age	
<50	13 (65)
≥50	7 (35)
Diagnosis	
AML	15 (75)
MDS	3 (15)
CML	0 (0)
ALL	2 (10)
Gender	
Male	9 (45)
Female	11 (55)
Time from first HCT to relapse	
<100 days	8 (40)
≥100 days	12 (60)
Time from first HCT to second HCT	
<1 year	12 (60)
≥1 year	8 (40)
Donor for first/second HCT	
Same	6 (30)
MRD-MRD	5
UBM-UBM	1
Different	14 (70)
UBM-UBM	4
MRD/CB-UBM	3
MRD/UBM-CB	6
Other	1
Conditioning for first/second HCT	
Myeloablative	8 (40)
Myeloablative-RIC	7 (35)
RIC-RIC	5 (25)
Stem cell source	
BM	8 (40)
PBSC	6 (30)
CB	7 (35)
Remission at second HCT	
No	9 (45)
yes	11 (55)
GVHD prophylaxis	
CSP-based	8 (40)
TAC-based	3 (15)
Others	3 (15)
GVHD	
No	10 (50)
Yes	10 (50)

HCT, hematopoietic cell transplantation; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ALL, acute lymphoid leukemia; MRD, matched-related donor; UBM, unrelated bone marrow; CB, cord blood; RIC, reduced-intensity conditioning; PBSC, peripheral blood stem cell; CSP, cyclosporin; TAC, tacrolimus.

nor, $n = 1$). Among the 15 patients who had received myeloablative conditioning for the initial HCT, eight received myeloablative conditioning and seven received RIC for the second HCT. The remaining five patients received both HCT with RIC. Although the 1-year OS after relapse was better in patients who received myeloablative conditioning for the second HCT than in patients who received RIC (100 vs. 37%, $P = 0.015$), patients who received myeloablative conditioning for the second HCT were younger and had a longer interval between the initial and the second HCT than those who received RIC ($P < 0.001$ and $P = 0.006$, respectively). There was no difference in OS between patients who received a second HCT from the same donor and those who had a different donor (1-year OS: 44 vs. 60%, $P = 0.48$).

Two patients underwent immediate HCT after relapse with concomitant graft failure. Among the other 18 patients who received reinduction chemotherapy before the second HCT, 11 had achieved CR at the second HCT and seven were not in CR. Four of the nine patients with nonremission disease at the second HCT, including two patients who did not receive reinduction chemotherapy, subsequently achieved CR; only one of the nine patients is currently alive in CR.

Of the 20 patients who underwent a second HCT, eight are alive with a median follow-up after relapse of 335 days (range: 181–997); five are in CR and three have recurrent disease.

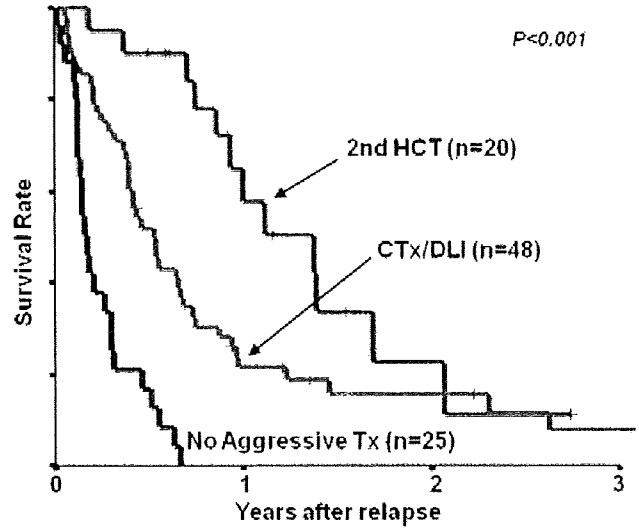

Figure 2. Overall survival. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

GVHD was newly diagnosed or interpreted to progress after the second HCT in 10 of the 20 patients. The median OS after relapse in patients with GVHD after the second HCT was 422 days (range: 181–997), and all of these patients achieved CR as a best response. The median OS after relapse for the remaining 10 patients without GVHD was 314 days (range: 66–757), and five of them failed to achieve CR as a best response.

Comparison of CR, NRM, and OS after relapse following the initial HCT

The median OS after the development of relapse in the 93 patients who had relapse/progression was 184 days (range: 5–1,456). Overall, 15 patients (16%) are currently alive with a median follow-up of 346 days (range; 33–1,456 days), and 10 of these patients are still in CR. Among the 78 patients who died, 69 died of disease progression and nine died of NRM (10%). The causes of NRM were GVHD and/or infection in eight (Cohort 1, one patient; Cohort 2, seven patients), and one early death after the second HCT with hepatic failure, which accounts for the one case of NRM for second HCT (Table II).

We compared the rate of CR, NRM, and OS after relapse among the three different cohorts (Table II). As the maximum response, the probabilities of achieving CR were 4% in Cohort 1, 38% in Cohort 2, and 75% in Cohort 3. The NRM rates were 4, 15, and 5% for each group, respectively. The median duration of remission after achieving CR was 177 days (range, 17–1,167). The median OS after relapse/progression in patients who underwent a second HCT (Cohort 3, 502 days) was significantly longer than those in Cohort 1 (61 days) and Cohort 2 (194 days, $P < .001$, Fig. 2). The 1-year OS after relapse was significantly better in patients with a second HCT (Cohort 3) than in the other patients (Cohorts 1 and 2) (58 vs. 14%). However, there was no significant difference in the 2-year OS, which suggests that it is difficult to maintain CR after a second HCT.

A multivariate analysis showed that CR after intervention (HR 3.83, 95% CI 2.06–7.11, $P < .001$), reinduction chemotherapy (HR 2.83, 95% CI 1.65–4.86, $P < .001$), a second HCT (HR 3.02, 95% CI 1.58–5.79, $P < .001$), and a longer time from the initial HCT to relapse (HR 1.99, 95% CI 1.21-3.28, $P = 0.007$) were associated with an improved OS after relapse/progression (Table V). Diagnosis, patient age at initial HCT, gender, conditioning regimen, or donor in the initial HCT and DLI were not significant factors.

TABLE V. Univariate and Multivariate Analysis of risk Factors for OS after Relapse

	Univariate analysis		Multivariate analysis	
Variables	HR (95%CI)	*P*	HR (95%CI)	*P*
Diagnosis			–	–
CML	1.00			
AML	2.03 (0.62–6.65)	0.241		
ALL	2.54 (0.71–9.00)	0.150		
MDS	3.39 (0.94–12.24)	0.062		
Age			–	–
<50	1.00			
≥50	1.53 (0.98–2.41)	0.063		
Gender			–	–
Male	1.00			
Female	0.92 (0.59–1.43)	0.701		
Conditioning			–	–
Myeloablative	1.00			
RIC	1.34 (0.84–2.12)	0.216		
Donor			–	–
MRD	1.00			
Others	1.26 (0.80–1.97)	0.322		
Disease Status at first HCT				
Standard	1.00			
High	1.23 (0.70–2.12)	0.465		
Time from first HCT to relapse				
≥100 days	1.00		1.00	
<100 days	1.74 (1.09–2.79)	0.020	1.99 (1.21–3.28)	0.007
Reinduction CTx				
Yes	1.00		1.00	
No	3.79 (2.24–6.40)	<.001	2.83 (1.65–4.86)	<.001
CTx Intensity			–	–
Reinduction	1.00			
Less Intensive	4.44 (2.00–9.88)	<.001		
DLI			–	–
Yes	1.00			
No	1.00 (0.57–1.72)	0.968		
Second HCT				
Yes	1.00		1.00	
No	2.89 (1.55–5.38)	<.001	3.02 (1.58–5.79)	<.001
CR after Interventions				
Yes	1.00		1.00	
No	3.54 (2.06–6.09)	<.001	3.83 (2.06–7.11)	<.001

OS, overall survival; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; RIC, reduced-intensity conditioning; MRD, matched-related donor; HCT, hematopoietic cell transplantation; CTx, chemotherapy; DLI, donor lymphocyte infusion; CR, complete remission.

Discussion

With this retrospective single-center survey in which we compared the outcomes of interventions for relapse/progression after allo-HCT, we showed that a second HCT significantly improved the remission rate and survival. In contrast to previous reports (8–13, 15), NRM after a second HCT was observed in an acceptable percentage of patients (5%), even though 40% of the patients received myeloablative conditioning regimen for the second HCT.

As salvage interventions for leukemia/MDS relapsing after allo-HCT, chemotherapy, DLI either alone or in combination, and second HCT have been considered with different degrees of success. Consistent with reports from other groups [1,4–6], we found that patients who did not undergo intensive chemotherapy had significantly shorter survival. Even though 43% of the patients who were given reinduction chemotherapy achieved CR, all of the relapsed patients who did not receive further intervention eventually relapsed unless relapse is isolated to CNS, and all but one patient died. Prior reports have also suggested that, instead of a certain probability of obtaining remission with reinduction chemotherapy, subsequent relapse is frequently observed and the prognosis is poor when further immunotherapy is suspended [1,4,6,19].

Although DLI has been recognized as an effective treatment for relapsed CML, the efficacy of DLI for relapsed acute leukemia is rather discouraging [3,7,20–22]. Although the remission rate has been reported to be 15–42%, the survival rate has not improved (3-year OS less than 20%), mostly because of a high incidence of uncontrolled GVHD (10–50%). In our cohorts, survival was not improved by adding DLI after chemotherapy, although half of the patients had achieved transient remission. The incidence of NRM after DLI was 29%, which was mostly explained by GVHD. Compared to DLI, a second HCT yielded an even better remission rate and lower NRM in our cohort, which could be respectively explained by the efficacy of the use of conditioning radiochemotherapy and GVHD prophylaxis in the second HCT.

In our data, a second HCT significantly improved the remission rate and survival compared to other interventions, as proven by a multivariate analysis. Although Arellano et al. [1] indicated that immunotherapy including a second HCT was effective compared to chemotherapy or supportive care, other reports that compared interventions after relapse following initial HCT failed to show the advantage of a second HCT [2,6,22]. Prior reports that focused on a second HCT have also expressed concerns about the negative impact of NRM, which has ranged from 24 to 75% (8–13, 15). In contrast, our data revealed a 5% incidence of NRM after a second HCT, which led to improved OS. This unexpectedly low incidence of NRM may reflect the advances in GVHD prophylaxis and supportive care over the past several years. Another possible explanation would be a selection bias of fitter patients that led to less NRM after the second HCT, although there were no significant differences in available characteristics of patients in each intervention group.

Concerning the conditioning regimen for the second HCT, we found that patients who received myeloablative conditioning had a better OS than patients who received

RIC. Eapen et al. [9] indicated the importance of a tumor-killing effect of myeloablative conditioning for the second HCT compared to RIC. Other groups also reported a superior outcome of TBI-based myeloablative conditioning in the second HCT [8,11]. On the other hand, several recent reports have shown that RIC offers a toxicity-reducing benefit in the second HCT [10]. In our cohort, patients who received myeloablative conditioning for the second HCT were younger and had a longer interval from the initial HCT to the second HCT, which could reflect a selection bias in the choice of myeloablative conditioning. Therefore, myeloablative conditioning for the second HCT could be considered beneficial for selected patients.

Consistent with several previous reports, we demonstrated that remission status [4,6,8–12,14,22,23], the use of reinduction chemotherapy [2,6], and a longer interval from the initial HCT to relapse [1,2,4,8–12,14,15,19,22–24] were associated with improved OS after relapse by multivariate analysis. Most prior reports have shown that an interval of 6 months or longer was associated with better OS. We found that patients who relapsed after 100 days following the initial HCT had better OS. However, relapses after intervals of 6 months or 1 year were not significantly associated with improved OS (data not shown).

Prior reports have also suggested that the development of GVHD after a second HCT [2,7–9,13,15,24] and the use of a different donor for the second HCT were associated with a better outcome after the second HCT [10]. Our data showed that both the remission rate and OS tended to be improved in patients who developed newly diagnosed GVHD after the second HCT. However, the use of a different donor for the second HCT did not appear to offer any advantage. Nevertheless, the small number of patients who received a second HCT in our study limits our ability to draw definite answers.

Although the 1-year OS after the second HCT was significantly better than that with other interventions (58 vs. 14%), there was no significant difference in 2-year OS (22 vs. 10%). The substantial decline in the survival curve in the second HCT group after 1 year from relapse was clearly related to recurrence of the underlying diseases. Previous reports also showed a decline in survival in the later period (<30% at 3–5 years from the second HCT) and a substantial relapse rate after the second HCT (>40%) [9–11]. This evidence suggests the need for the effective management of disease recurrence after the second HCT.

Our study is limited by several inherent selection biases. Most importantly, this is a retrospective study that compared the outcomes of interventions that were chosen at the discretion of physicians, although there were no significant differences in patient characteristics among the three cohorts. For example, patients who successfully received intensive intervention such as a second HCT had to survive long enough after relapse to be able to undergo adequate salvage chemotherapy with a rather controlled disease and less comorbidity. Other limitations include the small number of patients, a short follow-up period, and other transplant variables that may have affected the outcomes. Nevertheless, the present data in a consecutive-case series from a single center that reviewed various interventions after relapse allowed us to identify the factors that influenced the prognosis of patients with relapse/progression after allo-HCT.

In summary, these observations may have important implications for the selection of interventions in patients who relapse after allo-HCT. Our data indicated that reinduction chemotherapy with curative intent is required for prolonged survival, if feasible. However, when CR is not available with chemotherapy, long-term survival may be unlikely even with a second HCT. The second HCT may produce improved survival without excessive toxicity. However, the substantial incidence of a later relapse after the second HCT was revealed to be a major concern. Further studies are warranted to identify innovative post-transplant strategies to reduce disease recurrence, including immunotherapy such as a vaccination strategy.

References

1. Arellano ML, Langston A, Winton E, et al. Treatment of relapsed acute leukemia after allogeneic transplantation: A single center experience. Biol Blood Marrow Transplant 2007;13:116–123.
2. Bethge WA, Storer BE, Maris MB, et al. Relapse or progression after hematopoietic cell transplantation using nonmyeloablative conditioning: Effect of interventions on outcome. Exp Hematol 2003;31:974–980.
3. Collins RH Jr, Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol 1997;15:433–444.
4. Frassoni F, Barrett AJ, Granena A, et al. Relapse after allogeneic bone marrow transplantation for acute leukaemia: A survey by the E.B.M.T. of 117 cases. Br J Haematol 1988;70:317–320.
5. Mortimer J, Blinder MA, Schulman S, et al. Relapse of acute leukemia after marrow transplantation: Natural history and results of subsequent therapy. J Clin Oncol 1989;7:50–57.
6. Oran B, Giralt S, Couriel D, et al. Treatment of AML and MDS relapsing after reduced-intensity conditioning and allogeneic hematopoietic stem cell transplantation. Leukemia 2007;21:2540–2544.
7. Dazzi F, Fozza C. Disease relapse after haematopoietic stem cell transplantation: Risk factors and treatment. Baillieres Best Pract Res Clin Haematol 2007;20:311–327.
8. Bosi A, Laszlo D, Labopin M, et al. Second allogeneic bone marrow transplantation in acute leukemia: Results of a survey by the European Cooperative Group for Blood and Marrow Transplantation. J Clin Oncol 2001;19:3675–3684.
9. Eapen M, Giralt SA, Horowitz MM, et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. Bone Marrow Transplant 2004;34:721–727.
10. Hosing C, Saliba RM, Shahjahan M, et al. Disease burden may identify patients more likely to benefit from second allogeneic hematopoietic stem cell transplantation to treat relapsed acute myelogenous leukemia. Bone Marrow Transplant 2005;36:157–162.
11. Michallet M, Tanguy ML, Socie G, et al. Second allogeneic haematopoietic stem cell transplantation in relapsed acute and chronic leukaemias for patients who underwent a first allogeneic bone marrow transplantation: A survey of the Societe Francaise de Greffe de moelle (SFGM). Br J Haematol 2000;108:400–407.
12. Mrsic M, Horowitz MM, Atkinson K, et al. Second HLA-identical sibling transplants for leukemia recurrence. Bone Marrow Transplant 1992;9:269–275.
13. Radich JP, Sanders JE, Buckner CD, et al. Second allogeneic marrow transplantation for patients with recurrent leukemia after initial transplant with total-body irradiation-containing regimens. J Clin Oncol 1993;11:304–313.
14. Wagner JE, Vogelsang GB, Zehnbauer BA, et al. Relapse of leukemia after bone marrow transplantation: Effect of second myeloablative therapy. Bone Marrow Transplant 1992;9:205–209.
15. Kishi K, Takahashi S, Gondo H, et al. Second allogeneic bone marrow transplantation for post-transplant leukemia relapse: Results of a survey of 66 cases in 24 Japanese institutes. Bone Marrow Transplant 1997;19:461–466.
16. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21:4642–4649.
17. Saito K, Nakamura Y, Aoyagi M, et al. Low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor (CAG regimen) for previously treated patients with relapsed or primary resistant acute myelogenous leukemia (AML) and previously untreated elderly patients with AML, secondary AML, and refractory anemia with excess blasts in transformation. Int J Hematol 2000;71:238–244.
18. Yamada K, Furusawa S, Saito K, et al. Concurrent use of granulocyte colony-stimulating factor with low-dose cytosine arabinoside and aclarubicin for previously treated acute myelogenous leukemia: A pilot study. Leukemia 1995;9:10–14.
19. Pollyea DA, Artz AS, Stock W, et al. Outcomes of patients with AML and MDS who relapse or progress after reduced intensity allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2007;40:1027–1032.
20. Kolb HJ, Schmid C, Buhmann R, et al. DLI: Where are we know? Hematology 2005;10(Suppl 1):115–116.
21. Kolb HJ, Schmid C, Weisser M, et al. Cytoreduction, DLI, or mobilized peripheral blood progenitors. Ann Hematol 2002;81(Suppl 2):S30–S33.
22. Mielcarek M, Storer BE, Flowers ME, et al. Outcomes among patients with recurrent high-risk hematologic malignancies after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2007;13:1160–1168.
23. Levine JE, Braun T, Penza SL, et al. Prospective trial of chemotherapy and donor leukocyte infusions for relapse of advanced myeloid malignancies after allogeneic stem-cell transplantation. J Clin Oncol 2002;20:405–412.
24. Barrett AJ, Locatelli F, Treleaven JG, et al. Second transplants for leukaemic relapse after bone marrow transplantation: High early mortality but favourable effect of chronic GVHD on continued remission. A report by the EBMT Leukaemia Working Party. Br J Haematol 1991;79:567–574.

Bone Marrow Transplantation (2009) 44, 105–111

www.nature.com/bmt

ORIGINAL ARTICLE

Intensive glucose control after allogeneic hematopoietic stem cell transplantation: a retrospective matched-cohort study

S Fuji[1], S-W Kim[1], S Mori[1], S Kamiya[2], K Yoshimura[3], H Yokoyama[1], S Kurosawa[1], B Saito[1], T Takahashi[1], S Kuwahara[2], Y Heike[1], R Tanosaki[1], Y Takaue[1] and T Fukuda[1]

[1]*Department of Hematology and Stem Cell Transplantation, Tokyo, Japan;* [2]*Division of Nutritional Management, National Cancer Center Hospital, Tokyo, Japan and* [3]*Biostatistics and Epidemiology Section, Center for Cancer Control and Information Services, National Cancer Center Hospital, Tokyo, Japan*

Some studies have shown that intensive glucose control (IGC) improves outcome in the intensive care unit setting. However, it is the benefit of IGC in hematopoietic SCT (HSCT) that is not well defined. Between June 2006 and May 2007, IGC was maintained prospectively after allogeneic HSCT and clinical outcomes were compared with a cohort matched for conditioning regimen, source of stem cells, age and relation to donor. A stratified Cox regression model was used. There were no significant differences in baseline clinical characteristics. The median age was 43.5 years in both groups. The primary diagnosis was a hematologic malignancy. Patients in the IGC group had a lower glucose level (least-square mean, 116.4 vs 146.8 mg per 100 ml, $P<0.001$) compared to the standard glucose control group. The incidences of documented infections and bacteremia were significantly lower in the IGC group (14 vs 46%, $P=0.004$, 9 vs 39%, $P=0.002$, respectively). IGC tended to reduce the incidence of renal dysfunction (19 vs 37%, $P=0.36$) and the elevation of C-reactive protein (18 vs 38%, $P=0.13$). This study suggests that IGC has may have a beneficial effect after HSCT. IGC should be evaluated further in a large prospective, randomized study.

Bone Marrow Transplantation (2009) **44**, 105–111; doi:10.1038/bmt.2008.431; published online 19 January 2009
Keywords: intensive glucose control; allogeneic transplantation; hyperglycemia; C-reactive protein

Introduction

Previous studies showed that intensive glucose control (IGC), in which the target blood glucose level was set within 80–110 mg per 100 ml, reduced infections, dysfunction of organs including the liver and kidney and mortality compared to patients who received standard glucose control.[1–3] Although these results have been confirmed in several subsequent studies,[4–7] the precise mechanism that underlies this association is unclear. In animal models, it has been shown that insulin itself has a direct inhibitory effect on the inflammation process.[8,9] However in human studies, it has been suggested that these benefits could be directly attributed to IGC rather than to any pharmacological activity of administered insulin *per se*.[3,4]

Recipients of allogeneic hematopoietic SCT (HSCT), which is the most drastic therapeutic modality in patients with hematological malignancies, often suffer from serious complications including infectious diseases, GVHD and multiple organ failure. They are also at higher risk of hyperglycemia because of the use of steroids for the treatment of GVHD, the use of total parenteral nutrition (TPN), immunosuppressive drugs and infectious complications,[10,11] which makes them further susceptible to numerous serious complications including infectious diseases and multiple organ failure.[12–14] Our group previously reported that hyperglycemia during neutropenia was associated with an increased risk of acute GVHD and nonrelapse mortality (NRM) after myeloablative allogeneic HSCT,[15] and that hyperglycemia during neutropenia was associated with a higher incidence of subsequent acute GVHD. It is well known that an increase in the levels of circulating cytokines may aggravate hyperglycemia, and hyperglycemia itself could increase the levels of cytokines. This vicious cycle could lead to elevated cytokine levels, which could lead to subsequent acute GVHD. With this background, it can be hypothesized that IGC would reduce the incidence of infectious diseases, acute GVHD and organ dysfunctions after allogeneic HSCT. Therefore, we prospectively investigated the effect of IGC after allogeneic HSCT, and compared the clinical outcomes to those in a matched cohort to address whether IGC following allogeneic HSCT could improve the clinical course of patients, that is, reduction of infectious diseases and organ dysfunction, as has been shown in the intensive care unit (ICU) setting.

Correspondence: Dr Y Takaue, Department of Medical Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-Ku, Tokyo 104-0045, Japan.
E-mail: ytakaue@ncc.go.jp
Received 22 May 2008; revised 28 October 2008; accepted 21 November 2008; published online 19 January 2009

Patients and methods

Patients

From June 2006 to May 2007, a total of 73 patients received allogeneic HSCT at the National Cancer Center Hospital (Tokyo, Japan); 60 patients were eligible for participation in this trial. Finally, 22 patients (36.7%) were enrolled in this IGC study to keep the blood glucose level at 80–110 mg per 100 ml, as shown in Figure 1.

Study center and organization

The National Cancer Center Hospital in Tokyo holds 600 beds. The transplant team consists of 4 full-time physicians and 26 nursing staff who oversee 26 beds in the HSCT, and the entire ward is covered by high-efficiency particulate air-filters. We regularly perform 90–120 transplants per year: 80% allogeneic and 20% autologous.

Study design

This was a case–control study to investigate the clinical benefits of comprehensive nutritional support including IGC and parenteral nutrition (PN) management, which was approved by the Institutional Review Board. A matching control group was selected among patients who received HSCT from January 2002 to March 2007 (ratio of 1:2 compared to the study group) according to the following criteria: (1) conditioning regimen (conventional myeloablative or reduced intensity), (2) source of stem cells (BM, peripheral blood or cord blood), (3) age and (4) source of donor (related or unrelated). Criteria (1–4) were essential for inclusion. As a result, 42 matched controls were selected, and a total of 64 patients were subjected to further analysis (Table 1).

Exclusion criteria

Exclusion criteria were as follows: (1) patients who received a reduced-intensity conditioning regimen for an HLA-matched related donor, as we applied GVHD prophylaxis without short-term MTX in this setting, and they had much less need for TPN and less need for intense glucose control,[16] (2) those with a poor performance status (Eastern Cooperative Oncology Group) $\geqslant 2$, (3) those with uncontrolled infectious diseases at the beginning of the conditioning regimen and (4) those with preexisting neutropenia. We previously reported that the incidence of severe stomatitis (Common Terminology Criteria for Adverse Events (CTCAE) grade (3) was 0% after reduced-intensity SCT (RIST) from a related HLA-matched donor.[16] In this situation, the need for TPN and the incidence of hyperglycemia were quite low, compared to RIST from an unrelated donor, which included additional low-dose TBI or antithymocyte globulin (ATG) and short-term MTX or conventional SCT with a myeloablative regimen. Hence, we only included patients who received a RIST regimen from an unrelated donor, who had a higher probability of glucose-control intervention, to evaluate the beneficial effects of IGC.

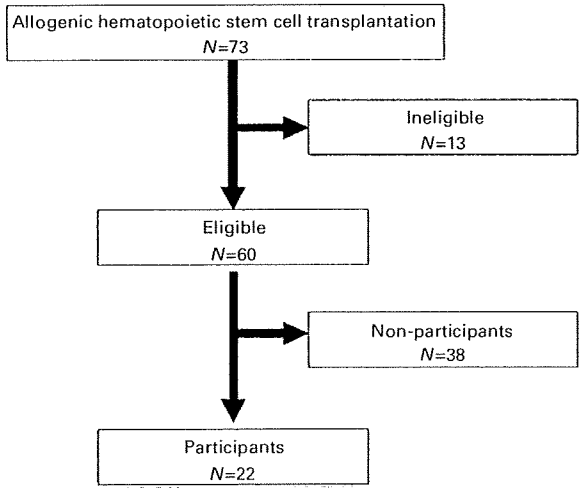

Figure 1 Trial profile.

Table 1 Patients' characteristics

Variable	N *(%)/median (range)*		P-*value*
	Intensive glucose control (n = *22*)	*Standard glucose control* (n = *42*)	
Age (years)	43.5 (17–64)	43.5 (20–66)	
<40	8 (36)	18 (43)	0.62
⩾40	14 (64)	24 (57)	
Sex			
Male	9 (41)	22 (52)	0.38
Female	13 (59)	20 (48)	
Disease risk[a]			
Standard	6 (27)	16 (38)	0.39
High	16 (73)	26 (62)	
Conditioning			
CST	14 (64)	27 (64)	
BU/CY	9 (40)	18 (43)	
CY/TBI (12 Gy)	4 (18)	6 (14)	
Other	1 (5)	3 (7)	
RIST	8 (36)	15 (36)	0.96
2CdA/BU	1 (5)	1 (2)	
Flu/BU	7 (32)	14(33)	
Low-dose TBI (2–4 Gy)	3 (14)	7 (17)	
Low-dose ATG	5 (23)	10 (24)	0.92
GVHD prophylaxis			
Cyclosporin-based	7 (32)	27 (64)	
Tacrolimus-based	15 (68)	15 (36)	0.01
Short-term MTX (+)	22 (100)	40 (95)	0.30
Relation to donor			
Related	6 (27)	12 (29)	
Unrelated	16 (73)	30 (71)	0.91
Stem cell source			
Bone marrow	15 (68)	30 (71)	
PBSC	5 (23)	10 (24)	
Cord blood	2 (9)	2 (5)	0.19
HLA match			
Match	11 (50)	28 (67)	
Mismatch	11 (50)	14 (33)	0.19

Abbreviations: ATG = antithymocyte globulin; 2CdA = cladribine; CST = conventional stem cell transplantation; Flu = fludarabine; RIST = reduced-intensity stem cell transplantation.
[a]Standard-risk patients included those with acute leukemia in first complete remission, chronic leukemia in first chronic phase, MDS in refractory anemia and NHL in complete remission, and the remaining patients were categorized as high risk.

Transplantation procedures

Forty-one patients received a myeloablative conditioning regimen that included BU (orally 4 mg/kg per day × 4 days or i.v. 3.2 mg/kg per day × 4 days) plus CY (60 mg/kg per day × 2 days, $n=27$), CY plus 12 Gy TBI ($n=10$) or other ($n=4$). Twenty-three patients received a reduced-intensity conditioning regimen that included fludarabine (30 mg/m^2 per day × 6 days) or cladribine (0.11 mg/kg per day × 6 days) plus BU (oral 4 mg/kg per day × 2 days or i.v. 3.2 mg/kg per day × 2 days). Low-dose TBI (2 or 4 Gy, $n=10$) and/or low-dose ATG (total dose 5–10 mg/kg ATG-F or 5 mg/kg thymoglobulin, $n=15$) were added. GVHD prophylaxis included CYA- ($n=13$) and tacrolimus-based regimens ($n=51$), with an additional short course of MTX. G-CSF was administered in all patients from day +6 after transplantation until engraftment. Most patients received ciprofloxacin (200 mg orally three times daily) for bacterial prophylaxis after the beginning of the conditioning regimen until neutrophil engraftment. Fluconazole (100 mg once daily) was administered for fungal prophylaxis after the beginning of the conditioning regimen. Low-dose acyclovir was given for prophylaxis against herpes simplex virus and VZV after the beginning of the conditioning regimen until immunosuppressive agents were discontinued. Prophylaxis against *Pneumocystis jiroveci* infection consisted of trimethoprim-sulfamethoxazole (400 mg of sulfamethoxazole once daily) from the first day of conditioning to day −3 of transplantation, and from day +28 until day +180 or the cessation of immunosuppressive agents. Patients who developed fever during the neutropenic period were treated with cefepime or other cephalosporin, and additional agents including vancomycin, aminoglycosides and amphotericin B were given as clinically indicated. Neutrophil engraftment was defined as the first of 3 consecutive days after transplantation that the ANC exceeded 0.5×10^9 per l.

Glucose management protocol

In the IGC group, the blood glucose level was routinely tested every morning to adjust the dose of insulin so as to keep the level within the range of 80–110 mg per 100 ml. Owing to the presence of fewer nursing staff in the HSCT unit than in the ICU, we replaced the continuous infusion of insulin with the addition of Humulin R to the bottle of PN to control the glucose level within the target range. In TPN, we universally added at least 1 unit of Humulin R per 10 g glucose. In patients who had an elevated blood glucose level, we also added Humulin R to the bottle of PN. We monitored the glucose level at least once a day in the morning as long as the level remained within the target range of 80–110 mg per 100 ml. When the glucose level became elevated, we increased the frequency of monitoring up to 2–4 times daily. In most patients, we adjusted the dose of insulin added to the bottle of PN as described in Table 2. When the blood glucose level was >180 mg per 100 ml or the dose of insulin was high, we manually adjusted the dose of Humulin R and administered insulin subcutaneously according to the attending physician's discretion. S.c. insulin administration usually consisted of 3–5 units at the beginning, and, if this was insufficient, the dose was manually adjusted by 2–4 units. When the patients received high-dose systemic steroid such as methylprednisolone 1–2 mg/kg per day for GVHD, we used the preprandial s.c. injection of insulin Aspart (NovoRapid) three times daily to avoid postprandial hyperglycemia and adjusted the dose according to the amount of food intake and the postprandial glucose level. When patients exhibited nausea, anorexia or vomiting, the amount of food intake became unstable. In such situations, insulin Aspart was injected immediately after the meal. When food intake was <50%, the dose was reduced or discontinued. Routine glucose monitoring was continued until PN was stopped, whereas the blood glucose level was maintained within the target range. Daily caloric intake was calculated by the dietitians. We tried to maintain oral intake as much as possible by using a suitable diet in jelly or liquid form. A dietitian adjusted the dose of supplemental PN to maintain the total caloric intake over 1.0 × basal energy expenditure (BEE), and if the glucose level was stable, the nutritional intake could be increased up to 1.5 × BEE. The glucose concentration in PN was usually started at 7.5% glucose as supplemental PN. The concentration was gradually increased to 12%, and, if necessary, this was further increased up to 18% to meet the target caloric intake. A lipid emulsion was also used to supply 10–30% of total caloric intake. The minimal total nutritional intake was set at 1.0 × BEE because a retrospective analysis at our institute showed that caloric intake of more than 1.0 × BEE was not associated with clinically significant wt loss.[17] To improve the glucose control, this level was set to be slightly lower

Table 2 Protocol for adjustment of Humulin R

Glucose level (mg per 100 ml)	*Adjustment of Humulin R*
BS ⩽ 40	i.v. 50% glucose 20 ml and recheck the glucose level Reduce the dose of Humulin R to 40–60% of the original dose
40 ⩽ BS < 60	i.v. 50% glucose 20 ml and recheck the glucose level Reduce the dose of Humulin R to 60–80% of the original dose
60 ⩽ BS < 80	i.v. 50% glucose 20 ml and recheck the glucose level Reduce the dose of Humulin R to 70–90% of the original dose
80 ⩽ BS ⩽ 110	No change
110 < BS < 130	Increase the dose of Humulin R to 110–120% of the original dose
130 ⩽ BS < 150	Increase the dose of Humulin R to 120–130% of the original dose
150 ⩽ BS < 180	Increase the dose of Humulin R to 130–150% of the original dose
BS ⩾ 180	Manually adjust the dose of Humulin R combined with sliding subcutaneous insulin administration

Abbreviation: BS = blood sugars.

than the recommendation in the HSCT setting (1.3–1.5 × BEE[18]). There are two beneficial aspects of this protocol: we could maintain the minimal caloric intake with supplemental PN and we could immediately start insulin as required after the introduction of PN. The SGC group was managed without a specific protocol for nutrition practice and glucose control, although we routinely monitored blood glucose at least three times weekly to avoid severe hyperglycemia (blood glucose >200 mg per 100 ml).

Outcome measures

Serially monitored glucose values were compared between the IGC group and the SGC group. We also analyzed the association between the mean glucose level during monitoring and the infection rate in both the SGC group and IGC group. Mean glucose levels were estimated for each patient and were categorized as follows: 80–110, 111–140, 141–179 and >180. Glycemic variability, defined as the s.d. of the mean glucose value, was also analyzed. The outcome measures were time to the occurrence of documented infectious complications within 100 days after HSCT, time to each organ dysfunction defined as described below, time to grades II–IV and grades III–IV acute GVHD and time to NRM. These were calculated from the date of the start of the conditioning regimen. Organ dysfunction was defined with reference to van den Berghe[5–7] as follows: (1) hypercreatininemia; serum creatinine level ⩾2.0 mg per 100 ml or more than twice the baseline, (2) hyperbilirubinemia; serum total bilirubin level ⩾2.0 mg per 100 ml and (3) increased inflammatory markers; serum C-reactive protein (CRP) level ⩾15 mg per 100 ml. In our institute, the CRP level was routinely monitored at least three times a week, as we previously reported that the preengraftment CRP level may predict a subsequent occurrence of acute GVHD and NRM after allogeneic HSCT.[19] These results suggested that CRP might be useful not only as a marker of infectious diseases but also as a surrogate marker for produced cytokines. Therefore, the serial changes of CRP level were compared between the two groups. Acute GVHD was graded by the consensus criteria.[20]

Statistical analyses

Baseline characteristics were summarized using descriptive statistics. The Student's t, χ^2 and Wilcoxon rank-sum tests were used to compare clinical and patient characteristics. The probability of documented infectious complications and organ dysfunction were calculated using Kaplan–Meier estimates. A stratified Cox regression model, which accounts for the matched-cohort design, was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). On the basis of 64 patients, the study has an approximately 80% power to detect a HR of 0.5 for documented infections. The glucose values, measured repeatedly, were compared between groups using a repeated-measure analysis with a linear mixed-effect model. A level of $P<0.05$ was defined as statistically significant. All P-values are two-sided. All analyses were performed using SAS version 9.1.3 (Cary, NC, USA).

Results

Patient characteristics

Table 1 lists the patients' clinical and transplantation characteristics. Patients and transplantation characteristics were well balanced with the application of matching criteria. Nevertheless, in the IGC group, more patients received tacrolimus for GVHD prophylaxis (68 vs 36%, $P=0.01$) and more had a previous transplantation (32 vs 7%, $P=0.01$). The median duration of follow-up in surviving patients was 299 days (range, 78–607 days) in the IGC group and 1146 days (range, 329–1774 days) in the SGC group.

Glycemic control

Duration of monitoring and number of tests. The median duration of glucose monitoring and intervention in the IGC group was 38 days (range, 24–70 days) after the start of the conditioning regimen. The total number of glycemic monitorings was 867 and 1094 in the SGC group and IGC group, respectively.

Mean values and distribution of values. Patients in the IGC group had a lower glucose level (least-square mean, 116.4 vs 146.8 mg per 100 ml, $P<0.001$) than the SGC group. The trend of the glucose value is shown in Figure 2a. All glycemic results for the SGC and IGC groups were stratified into six levels: <40, 40–79, 80–110, 111–140, 141–179 and ⩾180, as shown in Figure 2b.

Hypoglycemia

In the IGC group, the incidence of mild hypoglycemia (CTCAE grades 1–2, glucose level 40–69 mg per 100 ml) was significantly higher than that in the SGC group (11 vs 3 patients, $P<0.001$). Although one patient (4.5%) in the IGC group who was diagnosed as type 2 diabetes mellitus developed severe hypoglycemia (CTCAE grade 3, glucose level 30–39 mg per 100 ml) with faintness, no patient developed seizure or loss of consciousness.

Glycemic variability

The mean glycemic variability in the SGC group and IGC group was 37.2 mg per 100 ml (range, 10.1–121.7 mg per 100 ml) and 27.5 mg per 100 ml (range, 11.3–46.6 mg per 100 ml), respectively, and glycemic variability in the IGC group tended to be lower than that in the SGC group ($P=0.07$).

TPN and insulin dosing

The percentage of patients who received TPN was 60% (25 patients) and 77% (17 patients) in the SGC group and the IGC group, respectively. The mean duration of TPN was 9 days (range, 0–35) and 13 days (range, 0–38) in the SGC group and IGC group, respectively. There was a tendency for more patients in the IGC group to receive TPN compared to the SGC group, but this difference was not statistically significant. The mean maximal dose of insulin (median (range), 51 (0–100) vs 2 (0–110) IU, $P<0.001$) and the mean maximal dose of insulin per 1 g parenteral glucose

were significantly higher in the IGC group (median (range), 0.22 (0–0.71) vs 0.003 (0–0.4) IU/g glucose, $P<0.001$).

Infections

Table 3 summarizes the results. In the IGC group, dramatically fewer patients developed documented infections within 100 days compared to the SGC group, as shown in Figure 3.

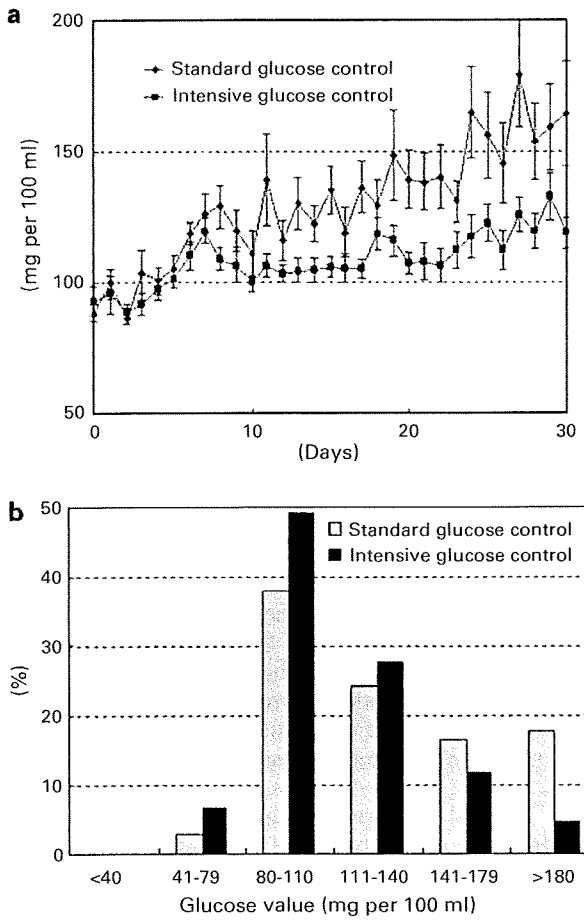

Figure 2 Serial changes in the mean glucose level in the intensive glucose control (IGC) and standard glucose control (SGC) groups. Values are mean + s.e. (**a**). The distribution of the glucose values in IGC and SGC is shown as a histogram (**b**).

Relation to mean glucose level

We also analyzed the association between the mean glucose level during monitoring and the infection rate in both the SGC and IGC groups. The incidence of infection was 34, 17, 67 and 40%, respectively, with mean glucose levels of 80–110, 111–140, 141–179 and ⩾180. When we compared a lower glucose-level group (mean glucose level of 80–140) with a higher glucose-level group (mean glucose level of >140), the incidence of infection was significantly higher in the latter group (28 vs 57%, $P=0.042$). When we assessed only patients with a lower glucose level, the IGC group tended to show a lower incidence of infectious diseases than the SGC group (14 vs 41%, $P=0.061$).

Relation to glycemic variability

We also analyzed the association between glycemic variability and the infection rate. The mean glycemic variability in patients with and without infection was 34.6 mg per 100 ml (range, 10.5–121.7 mg per 100 ml) and 33.3 mg per 100 ml (range, 10.1–110.6 mg per 100 ml), respectively, with no significant difference. As the importance of glycemic variability could vary among patients

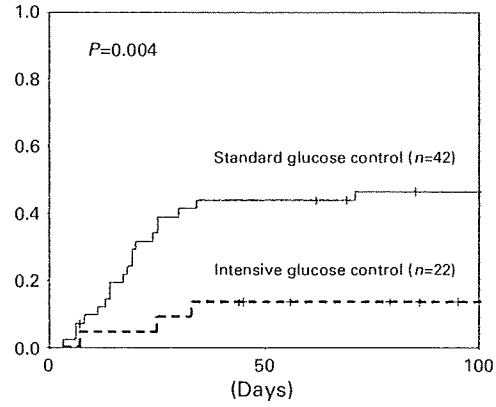

Figure 3 Probability of documented infections in the IGC and SGC groups.

Table 3 Incidence of infectious diseases and organ dysfunction

Variable	N *(%)/median (range)*			
	Intensive glucose control n = *22 (%)*	*Standard glucose control* n = *42 (%)*	*HR (95% CI)*	P-*value*
Documented infection	13	46	0.17 (0.04–0.75)	0.004
Bacteremia	9	39	0.10 (0.01–0.74)	0.002
Organ dysfunction				
Hypercreatininemia[a]	19	37	0.60 (0.19–1.88)	0.36
Hyperbilirubinemia[b]	28	31	1.05 (0.38–2.91)	0.93
Increased inflammatory markers[c]	18	38	0.45 (0.15–1.37)	0.13

Abbreviations: CI = confidence interval.
[a]Serum creatinine level ⩾2.0 mg per 100 ml or more than twice of baseline.
[b]Serum bilirubin level ⩾2.0 mg per 100 ml.
[c]Serum C-reactive protein level ⩾15 mg per 100 ml.