厚生労働科学研究費補助金　がん臨床研究事業

H19－がん臨床－一般－019

＜研究課題名＞

治療関連合併症を減少させて同種造血幹細胞移植後の生存率の向上を目指す標準的治療法の開発研究

平成 19 年度～平成 21 年度
総合研究報告書

研究代表者　　福田 隆浩

国立がんセンター中央病院

平成 22 年（2010 年）3 月

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Ⅰ．総合研究報告

厚生労働科学研究費補助金　がん臨床研究事業
平成19年度～21年度　総合研究報告書

『治療関連合併症を減少させて同種造血幹細胞移植後の生存率の向上を目指す標準的治療法の開発研究』

研究代表者　福田 隆浩　国立がんセンター中央病院／特殊病棟部 医長

研究要旨

移植片対宿主病（GVHD）や感染症などの治療関連合併症は、同種造血幹細胞移植成績の向上には克服すべき重要な課題である。GVHD治療薬である抗ヒトTリンパ球ウサギ免疫グロブリン（ATG）やミコフェノール酸モフェチル(MMF)、サイトメガロウイルス（CMV）感染症治療薬であるホスカルネットナトリウム水和物（FCN）などの薬剤は、海外では標準治療として広く用いられているが、国内では造血細胞移植分野における保険適応がない。本研究の目的は、これらの薬剤の我が国における適応外使用の現状を全国調査により明らかにし、効能追加に直結する多施設共同臨床試験を行い、我が国独自のエビデンスを確立することにより適応拡大を目指す。

A．研究目的

GVHDや感染症などの治療関連合併症は、同種造血幹細胞移植成績の向上には克服すべき重要な課題である。海外では、GVHDの予防・治療薬としてATGやMMFが、またCMV感染症に対してはFCNが標準治療薬の一環として広く用いられており、安全性・有効性に係るランダム化比較試験のエビデンスが蓄積されている。国内では、これらの薬剤の造血細胞移植分野における保険適応はないものの、重症のGVHDや感染症に対して適応外使用される頻度が増加し、適応拡大への要望が患者団体や移植医の間からも高まっている。しかし我が国では、対象患者が年間数千人と少なく当該企業のメリットも小さいため、治験による適応拡大が行われる見込みはない。

そこで本研究の目的は、これらの薬剤の我が国における適応外使用の現状を全国調査により明らかにし、効能追加に直結する多施設共同臨床試験を行い、日本人におけるエビデンスを確立することで適応拡大を図る。さらに、当該企業、医薬品医療機器総合機構(PMDA)、日本造血細胞移植学会と協働し、本研究成果と共に、国内外での使用状況と海外論文などの客観的データを総括し、2課長通知に基づいてこれらの薬剤の移植領域での効能追加、適応拡大の承認を得るための申請データ作成を目指す。この過程で、我が国の標準治療を確立させる。

抗がん剤を始めとする薬剤承認においては、標準的治療薬の根拠を海外データに頼ることも多いが、GVHDなどの同種免疫反応や薬物代謝のパターンは人種により大きく異なることが知られており、海外の臨床試験結果を日本人にそのまま当てはめるのは困難である。薬物動態検査も含めた本研究の詳細な解析は、これらの薬剤の我が国における至適用法・用量や安全性・有効性に関する貴重なエビデンスとなる独創的なものである。また造血幹細胞移植患者に対する栄養管理に関する研究は、日本では今までほとんど行われておらず、移植後の治療関連合併症を減少させる画期的な方法と考える。

本研究で行われる臨床研究のエビデンスを基盤にして、企業、行政、日本造血細胞移植学会が一体となり、これらの薬剤の移植領域での効能追加、適応拡大の承認を促進する新たなシステムのモデルを構築することは画期的と考える。

B．研究方法

（1）薬剤使用状況全国調査

日本におけるMMF（分担：鈴木）、FCN（分担：池亀・鈴木）、ATG（分担：畑中・鈴木）の適応外使用の現状および実際の用法・用量や安全性・有効性に関する情報を、日本造血細胞移植学会データベースを基盤とし全国アンケート調査を行った。

（2）GVHD・感染症に関する臨床試験

臨床統計家（分担：山口）の関与のもとに下記の臨床試験を行っている。

a) ATG

「非血縁者間同種骨髄移植におけるフルダラビン，静注ブスルファンおよび低用量 ATG による骨髄非破壊的前処置の安全性・有効性に関する多施設共同研究」（分担：福田）を作成し症例登録中である。

b) MMF

「GVHD 予防における MMF の至適投与法確立に関する薬物動態検査を用いた臨床試験（MMF 1 日 3 回投与による GVHD 予防の安全性・有用性の検討）」が進行中である（分担：松井）。高齢者における非血縁者間臍帯血ミニ移植後のタクロリムス(TAC)+MMF による GVHD 予防法の安全性・有用性に関する検討を行った（分担：谷口）。また薬物動態検査も含めた血縁者間同種移植および非血縁者間骨髄移植における「MMF 投与の急性 GVHD 予防効果に関する多施設共同第 II 相試験」（分担：中前・日野）を作成した。

c) ボリコナゾール(VRCZ), イトラコナゾール(ITCZ)

「造血幹細胞移植後 GVHD 発症患者における VRCZ または ITCZ 投与時の深在性真菌症発症予防効果（有効性と安全性）を検討する多施設共同無作為化非盲検臨床試験」（分担：神田）を作成し症例登録中である。

（3）造血幹細胞移植患者に対する栄養管理に関する研究

厳格血糖管理(IGC)と栄養療法の意義について後方視的に解析した結果を基にして「IGC 下における脂肪乳剤非投与群と投与群のランダム化第 II 相臨床試験（NST01 試験）」および「自家移植患者における synbiotics 非投与群と投与群のランダム化第 II 相臨床試験（NST02 試験）」（分担：金・福田）を作成し、症例登録中である。「造血細胞移植後の耐糖能に関する前方視的モニタリング研究（NST03 試験）」は症例登録が完了した。

（4）その他の研究

1）造血細胞移植後の慢性 GVHD に関する基礎的研究（分担：豊嶋）、2）免疫調整遺伝子多型の解析（分担：高見）、3）TAC を用いた非血縁骨髄移植後の効果的な GVHD 予防に関する研究（分担：森）、4）同種移植後の長期フォローアップ体制に関する実態調査（分担：萩原）、5）ヒトヘルペスウイルス 6 型(HHV-6)脳炎の克服を目標とした抗ウイルス療法の検討（分担：緒方）、6）非血縁骨髄ミニ移植後の非再発死亡の比較（分担：福田）。

＜倫理面への配慮＞

本研究を実施するにあたっては、ヘルシンキ宣言、米国ベルモントレポート等の国際的倫理原則、「臨床研究に関する倫理指針」（平成16年厚生労働省告示第459号）にのっとり、対象患者の人権を最大限に尊重してから行うこととする。説明同意文書を二部作製して対象患者本人に渡したうえで、内容を極力分かり易い言葉で説明し文書による同意を得る。この際に、患者の費用負担が増えることはないこと、この研究への参加は自由で参加しなくても不利益は受けないこと、この研究へ参加した場合でもいつでもやめられること、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報保護を厳守することも説明する。既に実施されている臨床試験と同様に、綿密な治療計画に基づいて ICH-GCP の精神に準拠した研究計画書を作成し、倫理審査委員会の承認を得て臨床試験登録を完了させた後に行うこととする。

C．研究結果

【1】FCN

血縁者間移植後に CMV 感染を合併して FCN 投与を受けた 320 例について詳細に解析し論文投稿した。61%の症例では FCN 使用前にガンシクロビル(GCV)が使用されていた。CMV 抗原血症に対する FCN 早期投与を受けた 248 例中、77%で消失、13%で改善を認め、CMV 感染症の breakthrough は認めなかった。腸炎などの CMV 感染症に対して FCN が投与された 65 例中、52%で症状の改善を認めた。Grade 3 以上の有害事象は電解質異常や血球減少が主なもので、腎機能障害は 3%に認めるのみであった。

本調査結果を参考資料として、厚労省および PMDA との計 5 回の面談結果を基にして、当該企業が平成 22 年 6 月に適応拡大申請を行う予定である。

また「HHV-6 による脳炎予防のための少量 FCN 投与試験」で予防投与を受けた 32 例の解析の結果、$>1x10^4$ copies/ml の高レベル HHV-6 再活性化は

Historical control 51 例よりも有意に少なく(12.5% vs 33.8%)、ＦＣＮ投与群では中枢神経症状は認めなかった(0% vs 11.8%)。

【２】ＭＭＦ

血縁者間移植後にMMF投与を受けた314例について詳細に解析した。約半数がGVHD予防としてMMFが投与され、従来の免疫抑制剤とほぼ同等の予防効果であった。約半数がGVHD発症後の二次治療としてMMFが投与され、急性GVHDの改善度は約５割、慢性GVHDの改善度は約２割であった。有害事象は好中球減少、血小板減少、感染症がそれぞれ14％に認められ、下痢が10％、悪心が6％で、重篤な有害事象は認めなかった。

臍帯血を用いたミニ移植において、TAC＋MMFとTAC単独のGVHD予防効果に関するMatched pair解析を行った。TAC＋MMF群では有意に好中球生着達成率が高く(90% vs 66%)、移植後30日以内の非再発死亡率が有意に低かった(0% vs 21%)。

薬物動態検査を基にしたMMFによるGVHD予防法確立に関する研究を行い、高い臨床効果が期待される活性代謝産物MPA濃度を維持するためには１日分３経口投与が必要なことを明らかにした。

造血幹細胞移植領域におけるMMFの適応拡大について厚労省研究開発振興課およびPMDAと事前面談を行った結果を基にして、薬物動態検査も含めた血縁者間同種移植（予定登録数：19例）および非血縁者間骨髄移植（予定登録数：29例）における「MMF投与の急性GVHD予防効果に関する多施設共同第II相試験」を作成した。

【３】ATG

血縁および非血縁者間移植時にATGを使用した177例について全国調査を行った。ATGの投与量は海外の報告と比較して少量にも関わらず、非血縁骨髄移植87例での重症急性GVHDは8.8％と低率であった。

非血縁骨髄ミニ移植を行う際に、欧米と比較して４分の1以下の低用量ATGを併用することにより、重症急性GVHDや非再発死亡を著明に減少させることを明らかにした。

この結果を基にして「非血縁者間同種骨髄移植におけるフルダラビン、静注ブスルファンおよび低用量ATGによる骨髄非破壊的前処置の安全性・有効性に関する多施設共同研究」を作成し、10施設でIRB承認を受け、11例が登録された（予定登録数：27例）。

ATGは同種移植後のGVHD予防として欧州で適応拡大の審査中であり、その申請資料と国内での調査結果を基にPMDAと面談を行った。

【４】真菌感染予防薬

致死的な真菌感染症のリスクが極めて高いGVHD合併患者を対象とした「VRCZまたはITCZ投与時の深在性真菌症発症予防効果を検討する多施設共同無作為化非盲検臨床試験」は、14施設でIRB承認を受け、16例が登録されている（予定登録数：各群33例、計66例）。

【５】造血幹細胞移植患者に対するIGC・栄養管理に関する研究

「IGC下における脂肪乳剤非投与群と投与群のランダム化第II相臨床試験（NST01）」は予定登録数の80例中47例が、また「自家移植患者におけるsynbiotics非投与群と投与群のランダム化第II相臨床試験（NST02）」は予定登録数の76例中16例が登録された。「造血細胞移植後の耐糖能に関する前方視的モニタリング研究（NST03）」は予定通り92例の登録が終了し、次年度に解析予定である。

H. 考察

MMFとFCNの薬剤使用状況全国調査は血縁者間移植を対象としていたことを考慮すると、国内の造血細胞移植患者での推定使用例数は各1000例以上と予想された。両薬剤とも有害事象は極めて軽微で、高い有効性と安全性が明らかになった。MMFの一日投与量は様々であったが、急性GVHD予防効果やGVHDに対する二次治療として用いた場合の改善率とも欧米と比較して遜色のない結果であった。また海外でもMMFの使用頻度が高い臍帯血ミニ移植において、TAC+MMFを用いたGVHD予防が移植後早期の非再発死亡を減少させ生着率を高めるという有望な結果を得た。薬物動態検査を基にしたMMFによるGVHD予防法確立に関する研究により、１日分３経口投与が有用であることを報告した。

本来は治験の枠組みでしか行われなかったPMDAとの対面助言を平成22年１月に行った結果、薬物動

態検査も含めたMMF予防に関する多施設共同臨床試験を施行後に適応拡大申請を行う方針となった。

CMV感染に対する第一選択薬はGCVであるが、GCVと同等の抗ウイルス効果を持ち造血抑制の副作用が少ないFCNは海外では標準治療として用いられている。近年、FCNの適応外使用例が急増しており、既に造血能が不十分であったり、GCV投与後の骨髄抑制が主な投与理由であった。特に造血回復が遅延しやすい臍帯血移植ではFCNの必要性は高く、移植領域での適応拡大が望まれる。FCNの適応拡大について厚労省・PMDAと計5回面談を行い、治験や臨床試験は行わず、平成22年6月に適応拡大の申請を行う予定である。

ICU領域では厳格血糖管理により感染症が減少するというエビデンスがあるが、本研究により同種造血細胞移植後も厳格血糖管理により感染症やGVHDのリスクが減少する可能性について、世界でも初めて報告した。

本研究により、造血幹細胞移植後のGVHDや感染症に関する我が国独自のエビデンスを確立し、オーファン領域における薬剤の適応拡大承認を促進する新らたなモデルシステムを構築することは極めて重要である。

E. 結論

GVHDや感染症などの治療関連合併症は、同種造血幹細胞移植成績の向上には克服すべき重要な課題である。海外では、ATG, MMF, FCN などの薬剤がGVHDや感染症に対する標準治療として広く用いられているが、我が国では対象患者が年間数千人と少ないため造血幹細胞移植領域での適応拡大が行われる見込みはない。そこで本研究の目的は、これらの薬剤の我が国における適応外使用の現状を全国調査により明らかにし、効能追加に直結する多施設共同臨床試験を行い、日本人におけるエビデンスを確立することで適応拡大を図る。

日本におけるMMF、FCN、ATGの使用状況全国調査を行ったところ、予想以上に多くの症例で適応外使用されていた。血縁者間移植のみで300例以上のMMFに関するデータを収集し、海外の報告と遜色のないGVHD予防・治療効果と高い安全性を確認した。高齢者に対する臍帯血ミニ移植では、MMF+TACを用いたGVHD予防により早期非再発死亡の減少と高い生着率が可能となった。FCN投与量は様々であったが、特徴的な腎障害の頻度は少なく、GCVとほぼ同等の有効性が明らかになった。既に厚労省・PMDAとも計5回面談を行い、本調査結果と海外のエビデンスを基にFCNの移植領域での適応拡大の申請を行う予定である。

ICU領域では厳格血糖管理により感染症が減少するというエビデンスがあるが、本研究により同種造血細胞移植後も厳格血糖管理により感染症やGVHDが減少することを明らかにした。栄養管理に関する3つの臨床試験を行った。

「非血縁者間同種骨髄移植における低用量ATG-Fを併用したミニ移植試験」と「VRCZまたはITCZを用いた深在性真菌症発症予防試験」は現在も症例登録中であるが、造血幹細胞移植をより安全に行うために重要な臨床試験であると考えている。

本研究により、同種造血幹細胞移植後のGVHDや感染症に関する我が国独自のエビデンスを確立し、治療関連合併症を減少させることにより移植後の生存率向上を目指す。

F. 健康危機情報

該当事項なし

G. 知的財産権の出願・登録状況

該当事項なし

Ⅱ．主な研究成果（論文発表）一覧

研究成果の刊行物（論文別刷）

＜ 主な研究成果（論文発表）一覧 ＞

著者名（研究者にｱﾝﾀﾞｰﾗｲﾝ）	論文タイトル	発表誌名	巻号	ページ	出版年
Fuji S, **Kim SW**, Mori S, Furuta K, Tanosaki R, Heike Y, Takaue Y, **Fukuda T**.	Decreased insulin secretion in patients receiving tacrolimus as GVHD prophylaxis after allogeneic hematopoietic SCT.	Bone Marrow Transplant	45	405-406	2010
Kurosawa S, **Fukuda T**, Tajima K, Saito B, Fuji S, Yokoyama H, **Kim SW**, Mori SI, Tanosaki R, Heike Y, Takaue Y.	Outcome of 93 patients with relapse or progression following allogeneic hematopoietic cell transplantation.	Am J Hematol	84	815-820	2009
Fuji S, **Kim SW**, Mori S, Kamiya S, Yoshimura K, Yokoyama H, Kurosawa S, Saito B, Takahashi T, Kuwahara S, Heike Y, Tanosaki R, Takaue Y, **Fukuda T**.	Intensive glucose control after allogeneic hematopoietic stem cell transplantation: a retrospective matched-cohort study.	Bone Marrow Transplant	44	105-111	2009
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著者名（研究者にｱﾝﾀﾞｰﾗｲﾝ）	論文タイトル	発表誌名	巻号	ページ	出版年
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LETTER TO THE EDITOR

Decreased insulin secretion in patients receiving tacrolimus as GVHD prophylaxis after allogeneic hematopoietic SCT

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As it has been reported that hyperglycemia is associated with a higher risk of non-relapse mortality after allogeneic hematopoietic SCT (HSCT), the efficient control of hyperglycemia has become an important consideration for safer HSCT.[1–3] A characteristic feature of this field is the use of calcineurin inhibitors, including tacrolimus (TAC), which may cause hyperglycemia as suggested in organ transplant settings, possibly by decreasing insulin secretion.[4] To evaluate this possibility, we serially monitored fasting glucose levels and serum immunoreactive insulin, and calculated homeostasis model assessment (HOMA)-IR and HOMA-β with the HOMA model[5] as recommended by Wallace *et al.*[6] HOMA-IR reflects insulin resistance and HOMA-β reflects the insulin secretion status.[5] If HOMA-IR increased after the administration of allogeneic HSCT, drugs that reduce insulin resistance, such as metformin or pioglitazone, might theoretically be effective. In contrast, if HOMA-β decreased, drugs that increase insulin secretion, such as glucagon-like peptide-1 analog or sulfonylureas, might be effective. The data from this study may help us to better understand how we should control glucose levels after HSCT.

Data obtained from 43 adult patients who received allogeneic HSCT from October 2006 to December 2007 were included in the analysis. The median age of the patients was 48 years (range: 19–66 years). When patients were not receiving s.c. long-acting insulin, systemic corticosteroid or parenteral nutrition, blood samples were obtained 1–2 months after HSCT. GVHD prophylaxis was started using CsA-based ($n=13$) or TAC-based regimens ($n=30$), with an additional short course of MTX in 35 patients. At the time of subsequent blood sampling, 15 patients were receiving CsA and 28 patients were receiving TAC, with no significant difference in various factors including age, gender, disease and intensity of the conditioning regimen (conventional vs reduced intensity), except that the TAC group included more HSCT with unrelated BM than the CsA group (89 vs 27%, respectively). The results regarding fasting glucose level, immunoreactive insulin and the HOMA model are summarized in Table 1.

We found that HOMA-β was significantly reduced in the TAC group compared with that in the CsA group, which was consistent with earlier studies in an organ transplant setting.[4] Clinically, it has been reported that GVHD prophylaxis with TAC is generally associated with a reduced incidence of acute GVHD compared with CsA. In contrast, hyperglycemia was associated with a higher risk of non-relapse mortality after allogeneic HSCT.[1,3] In our earlier study, patients with severe hyperglycemia had a significantly higher incidence of acute GVHD compared with normoglycemic patients.[3] Therefore, it is possible that hyperglycemia related to the use of TAC could offset the potential benefit of TAC, and drugs that increase insulin secretion, including the glucagon-like peptide-1 analog, may reverse the suppression of the insulin level.[7] Whether intensive glucose control could reduce the risk of acute

Table 1 Pretransplant and posttransplant glycemic status

Variable	N *(%)/ Median (range)*			
	Tacrolimus (n = *28*)		*CsA* (n = *15*)	
Fasting glucose level (mg per 100 ml)				
Pretransplant	87 (80–129)	$P=0.08$	89 (79–154)	$P=0.55$
Posttransplant	95 (79–129)		91 (80–116)	
Immunoreactive insulin level (μU/ml)				
Pretransplant	6.1 (1.6–17.3)	$P=0.60$	6.6 (2.9–13.5)	$P=0.25$
Posttransplant	6.5 (1.5–18.0)		5.3 (2.4–10.1)	
HOMA-IR				
Pretransplant	1.4 (0.3–4.6)	$P=0.75$	1.4 (0.6–5.13)	$P=0.40$
Posttransplant	1.5 (0.3–4.2)		1.3 (0.5–2.2)	
HOMA-β				
Pretransplant	90.9 (30.3–193.7)	$P=0.04$	65.4 (38.7–160.0)	$P=0.43$
Posttransplant	69.9 (15.8–202.5)		61.7 (28.5–180.0)	

Abbreviations: HOMA = homeostasis model assessment; IR = insulin resistance.

GVHD in patients using TAC should be evaluated by prospective randomized control trials.

In conclusion, this is the first study to assess the change in the glycemic status with the HOMA model in patients undergoing HSCT with CsA or TAC. We showed that GVHD prophylaxis with TAC was associated with decreased insulin secretion and a resultant tendency for hyperglycemia. It is possible that measures to keep insulin and glucose levels within their respective normal ranges are effective for reducing morbidity and mortality after HSCT.

Conflict of interest

The authors declare no conflict of interest.

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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.

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Conflict of interest: Nothing to report.

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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.

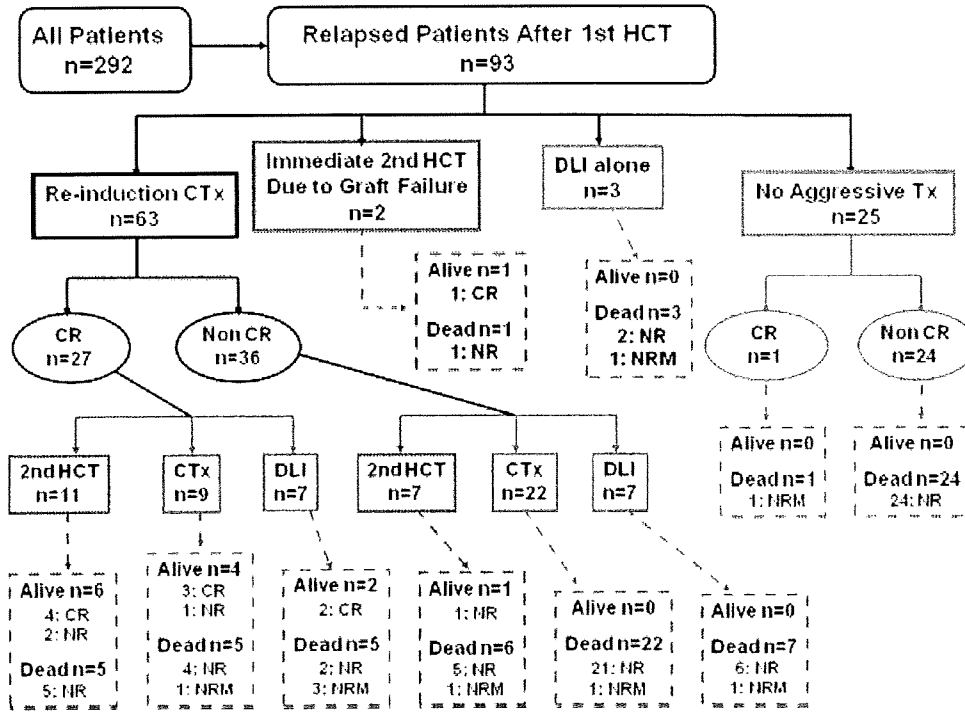

Figure 1. Summary of interventions after relapse. Abbreviations: HCT, hematopoietic cell transplantation; CTx, chemotherapy; Tx, therapy; CR, complete remission; DLI, donor lymphocyte infusion; NR, nonremission; NRM, nonrelapse mortality. [Color figure can be viewed in the online issue, which is available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

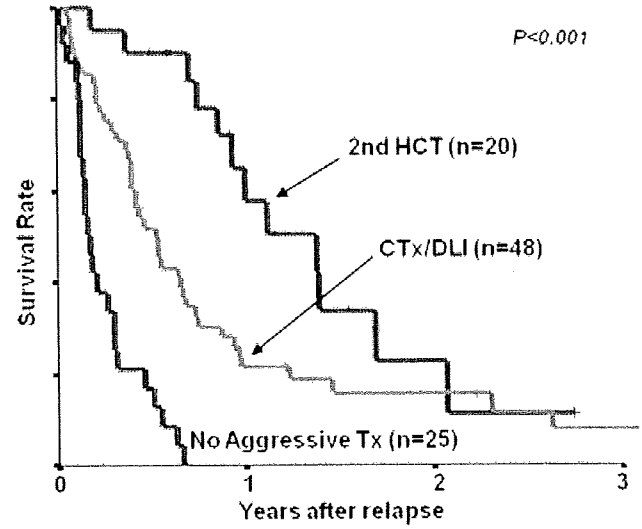

Figure 2. Overall survival. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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

Variables	Univariate analysis		Multivariate analysis	
	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.

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ORIGINAL ARTICLE

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

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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.

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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.

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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.

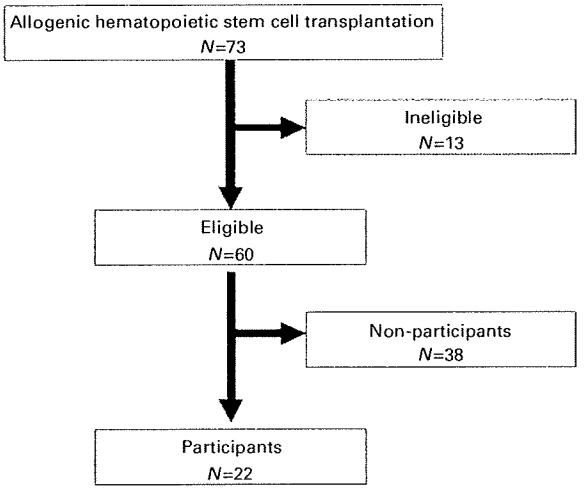

Figure 1 Trial profile.

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.