析により抽出した。

C．研究結果

①拒絶　4例。4例ともHLA mismatch症例。再移植を3例に施行。②生着までの日数－好中球数500／μl以上は中央値が113（8－21日）③発熱日数　平均2．8日（1日－6日）④GVHD　2度以上67％⑤サイトメガロウイルス陽性までの日数－中央値day 32、CMV陽性率（HRP-C7）80.9％。CMV病－3例（CMV-IP　1例、CMV網膜炎2例）⑥死亡原因：再発8例。GVHD 3例。GVHD+感染2例。⑦早期死亡（100日以内死亡／総死亡例）－7／17（41％）　すべてhigh risk症例。⑧移植関連死亡：100日で5例。1年で9例。⑨再発死亡：100日で2例。1年で8例。

表1に生存している8例の背景を示した。年齢は40歳以上で、診断から移植までの期間に関係なく、長期生存の因子は図1のように、移植時期が標準リスクであることであった。

D．考　察

信頼性の高い統計解析のために、さらに症例数の蓄積が必要である。

E．結　論

移植病期が標準リスクであれば有意に長期生存が期待出来る。

F．研究発表：別紙1
　論文発表：別紙2

G．知的財産権の出願・登録状況
　該当なし

図1．生存に関する危険因子の統計解析

Non-Parametric

Factor	Test	Chi−Sq	p-value
DONOR	Log-Rank	0.0071457	0.9326334
	Wilcoxon	0.1929224	0.6604954
GVHD	Log-Rank	0.0034562	0.9531199
	Wilcoxon	0.0207373	0.8854968
ATL	Log-Rank	1.4067587	0.2355952
	Wilcoxon	0.438009	0.508085
HLA	Log-Rank	1.9677064	0.1606915
	Wilcoxon	1.8947368	0.1686686
RISK	Log-Rank	5.747645	0.0165108
	Wilcoxon	4.725	0.0297272
AGE	Log-Rank	1.2731702	0.2591728
	Wilcoxon	0.5555556	0.4560565
SEX	Log-Rank	3.298072	0.0693613
	Wilcoxon	1.8846154	0.1698105

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分担研究報告書

「同種造血幹細胞移植後の呼吸器合併症に対する気管支鏡検査の有用性についての検討」

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2）　同　　血液科

研究要旨：2000年１月より2004年12月までの５年間に当院で造血幹細胞移植を実施した299例中、呼吸器合併症を発症し気管支鏡検査を施行した症例を対象に、その有用性について検討した。気管支鏡検査は39例（男性27例、女性12例）で合計45回施行されており、患者の年齢中央値は49歳（16－70歳）で、同種骨髄移植12例、同種末梢血幹細胞移植14例、同種臍帯血移植13例であった。気管支鏡検査が施行された時期は、移植後30日未満が６回（13.3％）、移植後30－100日が17回（37.8％）、移植100日以降が22回（48.9％）であった。検査内容は、気管支洗浄のみが12回、気管支肺胞洗浄（BAL）が28回、ブラッシングが３回、経気管支肺生検（TBLB）が７回であった。診断率は55.6％（25／45回）で、感染性呼吸器合併症が84％（21回）、非感染性呼吸器合併症が16％（４回）であった。気管支鏡施行時の検査内容による診断率は、TBLBが施行できた例で高く（５／７回：71.4％）、BALや気管支洗浄のみでは低い（それぞれ、14／28回：50％、６／12回：50.0％）傾向が認められた。造血幹細胞移植後の肺合併症における気管支鏡検査は、原因診断が得られ、新たな治療法決定にあたって有用と考えられた。

A．研究目的

血液疾患の治療として造血幹細胞移植は広く普及している(1)が、呼吸器合併症は、頻度が高く予後は不良となることも多い重大合併症である(2)。しかしながら、血液検査や画像による呼吸器合併症の診断には限界があるため、確定診断のために気管支鏡検査が施行される機会が多い。そこで、造血幹細胞移植後の呼吸器合併症における気管支鏡検査の有用性と限界について明らかにするため、本研究を実施した。

B．研究方法

2000年１月より2004年12月までの５年間に、当院で造血幹細胞移植を施行した299例の中で呼吸器合併症を発症し気管支鏡検査を施行した症例を対象とした。気管支鏡検査の内容は、個々の患者に応じて、病変の分布や全身状態、血小板数などを考慮し決定した。気管支鏡検査の有用性については、診療録の記載より主治医判断に基づいてレトロスペクティブに解析した。

C．結果

対象とした患者は、39例（男性27例、女性12例）で、年齢中央値49歳（16－70歳）であった。基礎疾患は、急性骨髄性白血病11例、骨髄異形成症候群６例、非ホジキンリンパ腫５例、慢性骨髄性白血病５例、急性リンパ性白血病２例、成人Ｔ細胞性白血病　２例、ホジキン病　２例、その他６例であった。移植の種類とし

ては、同種骨髄移植が12例、同種末梢血幹細胞移植が14例、同種臍帯血移植が13例であった。

気管支鏡検査は、39例に対して合計45回行われており、3回施行したのが1例、2回施行したものが4例であった。気管支鏡を施行したのは、移植後中央値97日（移植後10－610日）であった。移植後30日未満の早期が6回（13.3%）で、移植後 30－100日が17回（37.8%）、移植後100日以降の晩期が22回（48.9%）であった。

検査内容は、気管支肺胞洗浄（BAL）を行なったものが最も多く28回で、気管支洗浄のみが12回、ブラッシングが3回、経気管支肺生検（TBLB）が7回であった。

造血幹細胞移植後の呼吸器合併症に対する気管支鏡検査の診断率は、55.6%（25回／45回）であった。この中で、感染性呼吸器合併症88.0%（22回）であり、非感染性呼吸器合併症は12.0%（4回）であった。気管支鏡検査で診断可能であった疾患は、サイトメガロ肺炎やRSウイルス肺炎などウイルス性肺炎が7回（28%）で最も多く、次いで、アスペルギルス肺炎やカンジダ肺炎などの真菌性肺炎が6回（24%）、抗酸菌感染と*Pneumocystis* 肺炎がそれぞれ4回（16%）、細菌性肺炎が2回（8%）であった。一方、非感染性疾患は4回で間質性肺炎が1例で、びまん性肺胞出血が1例であった。

気管支鏡検査の内容による診断率は、BALが50.0%（14回／28回）、気管支洗浄のみが50.0%（6回／12回）であり、ブラッシングが66.7%（2回／3回）、TBLBは71.4%（5回／7回）と、少数例ながら生検を行なった方が、診断率が高い傾向があった。

D．考察

造血幹細胞移植後の呼吸器合併症に対する気管支鏡検査の有用性については、1985年以来幾つかの報告（3－12）がある。ほとんどの検討においてはBALが実施されており、多くは100回に満たない少数例の検討であったものの、その診断率は31 － 80%であった。とくに、臨床的に呼吸器感染症や肺胞出血の疑われる症例において、その有用性は確立されている(11)。われわれの検討では、気管支洗浄やBAL、TBLBなど症例によって検査の種類は異なっていたが、その診断率は55.6%と従来の同様の報告とほぼ同様であった。

われわれの検討では、ブラッシングあるいはTBLBを施行した患者において、診、k見断率が高い傾向があり、とくに非感染性の呼吸器合併症の診断において有用性が示唆された。しかし、Patelら(12)の検討では、169例の検討で71例にTBLBを施行したが、82%が非特異的所見のみであり、BALに加えて新たな情報が得られたのは10%未満であった。このため、彼らは造血幹細胞移植の呼吸器合併症に対する気管支鏡検査は、BALだけで十分であり、その診断率と出血などの合併症を考慮すると、TBLBは推奨できないとしている。

また、彼らは気管支鏡検査結果が治療方針に与える影響も検討している。気管支鏡検査で特異的な診断が得られた場合、70%の患者において、抗菌薬の中止や追加、あるいは、ステロイドの追加などの治療の変更が行われていた。一方、特異的な所見が得られなくても、30%の患者において治療の変更が行われた。このことは、造血幹細胞移植の呼吸器合併症の場合、気管支鏡検査で特異的な所見が得られなくても、感染性か非感染性か、すなわち、抗菌治療を強化すべきかステロイドを投与すべきかの判断に、特異的な所見の得られないBAL（negative BAL）であっても有用であることを示すものと考える。造血幹細胞移植の呼吸器合併症の気管支鏡検査において、その原因診断が得られるのは50－60%ではあるが、治療方針の決定にはそれ以上に有用と考える。

一方、造血幹細胞移植後の呼吸器合併症の診断において、開胸あるいは胸腔鏡下肺生検は、侵襲の大きさため適応が大きく限られる(13)が、これと比較して、気管支鏡は比較的侵襲の小さい検査である。とくに呼吸不全のために気管内挿管された患者においては、その実施は容易である。

造血幹細胞移植の呼吸器合併症の診断における限界としては、とくに非感染性肺合併症の診断が困難であることが挙げられる。器質化肺炎、間質性肺炎はTBLBで病変が採取されれば診断可能なこともあるが、診断困難であることも少なくない。閉塞性細気管支炎の診断においては、障害を受ける細気管支領域を

TBLBで採取することは困難であり、気管支鏡検査の診断的価値は低い。また、開胸肺生検と比較すると侵襲は小さいとは言え、侵襲的な検査であるため、全身状態や呼吸状態が不良のため、気管支鏡が施行できない患者も少なくない。造血幹細胞移植後は、多くの症例において血小板が減少しているため、TBLBのみならず、気管支鏡自体を実施することが困難なこともある。更に。アウトカムとして生存率の改善を証明したスタディはなく（3－12)、実施にあたっては慎重な患者の選択が必要と思われる。

以上、造血幹細胞移植後の呼吸器合併症に対する気管支鏡検査は、特異的な診断が得られなくても治療方針の決定にあたって有用である。このため、その有用性と限界について理解した上で、適切な症例を選択して実施すべきである。

E．結論

1．造血器幹細胞移植後の呼吸器合併症の診断において気管支鏡検査は有用であり、とくに感染性呼吸器合併症の場合に診断がつきやすく、原因微生物も特定できるため有用性が高いと考えられる。

2．診断率は約55％と従来の報告と同程度であったが、negative BALでも治療方針の決定に際して有用であり、適応のある症例では積極的に試みるべきと考えられる。

F．健康危険情報

造血幹細胞移植後の呼吸器合併症の診断に気管支鏡検査は有用である。検査内容として、BALに加えてTBLBを実施すべきかについては未だ明らかでない。造血幹細胞移植後の呼吸器合併症に対する気管支鏡検査の実施は、アウトカムとして生存率の改善を証明した報告はなく、これを踏まえて慎重に対象患者を選択して実施することが必要である。

G．研究発表

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H．知的財産権の出願・登録状況（予定を含む）

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

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Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

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Comparison between reduced intensity and conventional myeloablative allogeneic stem-cell transplantation in patients with hematologic malignancies aged between 50 and 59 years

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Summary:

To evaluate the efficacy of reduced-intensity stem-cell transplantation (RIST), we retrospectively compared outcomes of 207 consecutive Japanese patients aged between 50 and 59 years with hematologic malignancies who received RIST ($n=70$) and conventional stem-cell transplantation (CST) ($n=137$). CST recipients received total body irradiation (TBI)-based or busulfan/cyclophosphamide-based regimens. RIST regimens were purine analog-based ($n=67$), 2 Gy TBI-based ($n=2$), and others ($n=1$). Most CST recipients (129/137) received calcineurin inhibitors and methotrexate as graft-versus-host (GVHD) prophylaxis, while 32 RIST recipients received cyclosporin. In all, 23 CST and five RIST recipients died without disease progression within 100 days of transplant. Grade II to IV acute GVHD occurred in 56 CST and 38 RIST recipients. There was no significant difference in overall survival (OS) and progression-free survival between CST and RIST. On multivariate analysis on OS, five variables were significant: preparative regimens (CST *vs* RIST) (hazard ratio = 1.92, 95% confidence interval, 1.25–2.97; $P=0.003$), performance status (2–4 *vs* 0–1) (2.50, 1.51–4.16; $P<0.001$), risk of underlying diseases (1.85, 1.21–2.83; $P=0.004$), acute GVHD (2.57, 1.72–3.84; $P<0.001$), and CML (0.38, 0.21–0.69; $P=0.002$). We should be careful in interpreting results of this small-sized retrospective study; however, reduced regimen-related toxicity might contribute to better survival in RIST. The low relapse rates following RIST suggest a strong antitumor activity through allogeneic immunity.
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Keywords: allogeneic hematopoietic stem-cell transplantation; regimen-related toxicity; graft-versus-host disease; nonrelapse mortality; graft-versus-leukemia effect

Allogeneic hematopoietic stem-cell transplantation (autologous stem-cell transplantation (allo-SCT)) is a therapeutic option for advanced hematologic malignancies. A small but significant proportion of these patients can be cured with allo-SCT.[1] Conditioning regimens have been developed to maximize dose intensity, escalating the dose-limiting toxicity in nonhematopoietic tissues.[2] Conventional stem-cell transplantation (CST) using a myeloablative preparative regimen is associated with severe regimen-related toxicities (RRT), resulting in high nonrelapse mortality (NRM) especially for old patients.[3] NRM tends to be higher in patients with refractory or advanced diseases, who have been treated heavily, compared with those who have achieved remission.[3] Considering that high-dose chemotherapy followed by allo-SCT is ineffective for these patients,[4] and that intensification of preparative regimens usually leads to severe RRT and high NRM,[5] it remains unknown whether myeloablative preparative regimens are beneficial to improve survival of patients with advanced chemorefractory leukemia.

A new strategy for transplantation using a reduced-intensity stem-cell transplantation (RIST) or nonmyeloablative preparative regimen has been developed to reduce RRT while preserving an adequate antileukemia effect.[4–6] This strategy decreases the risk of NRM and allows transplantation in elderly patients or those with organ

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dysfunction. RIST appears to be promising for a variety of hematologic diseases, if disease activity is controlled prior to transplant.[7] Most physicians believe that RIST is insufficient in controlling advanced hematologic malignancies, and that intensification of preparative regimens is required to improve their prognosis. Small pilot studies showed that RIST had been unsuccessful for advanced hematologic malignancies,[5,8] yet, efficacy of RIST has not been fully evaluated. Few comparative studies have been reported between RIST and CST for hematologic malignancies.[9]

Patients older than 50 years are regarded as candidates for RIST, yet, patients younger than 60 years frequently undergo CST. Either RIST or CST is offered to patients aged between 50 and 59 years according to doctors' preferences or based on patients' conditions. To evaluate the efficacy of RIST for hematologic malignancies in the elderly patients, we retrospectively compared the outcomes of 207 consecutive patients aged between 50 and 59 years with hematologic malignancies who had received either RIST ($n=70$) or CST ($n=137$).

Patients and methods

Data collection

We conducted a nation-wide retrospective survey of 207 adult Japanese patients aged between 50 and 59 years who received allo-HSCT from an HLA-identical sibling for the treatment of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and myelodysplastic syndrome (MDS) from February 1998 to November 2002 in 55 participating hospitals. Patients with a history of previous transplantation were excluded from this study.

All the CST and RIST recipients who were eligible in this study were included in each hospital. In Japan, approximately 2000 transplants are performed annually. The types of transplantations are autologous (40%), myeloablative allogeneic (45%), and reduced intensity or nonmyeloablative allogeneic transplantation (15%).[10] RIST recipients are generally treated as clinical studies in Japan. Most patients were incurable with conventional treatments and were considered inappropriate for conventional allo-SCT because they were age >50 years old and/or due to organ dysfunction (generally attributable to previous intensive chemo- and/or radiotherapy).

Data from participating centers were derived from questionnaires distributed to each center. Minimum data required for the inclusion of a patient in this study were age, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) criteria before conditioning, medical complications at transplant, diagnosis of underlying diseases, treatment prior to allo-HSCT, disease status at transplant, preparative regimens, GVHD prophylaxis, date of transplant, date of follow-up, disease status at follow-up, development of acute and/or chronic GVHD, date of acute and/or chronic GVHD, date of disease progression/death, and causes of death. We have not collected information on the types of chronic GVHD (limited *vs* extensive).

Definition

Reduced-intensity regimens were defined as reported previously.[11,12] The upper limits of busulfan, melphalan, and TBI were 8, 140 mg/m^2, and 2 Gy for consideration as reduced-intensity preparative regimens. Neutrophil recovery was defined as an absolute neutrophil count of more than 0.5×10^9/l for two consecutive days. Patients were divided into two groups based on their disease status at transplant. Low-risk patients were defined as those with acute leukemia in first remission, CML in chronic phase, and myelodysplastic syndrome refractory anemia. The others were classified into the high-risk group. NRM was defined as death without progression of the underlying disease. Overall survival (OS) was defined as the duration of survival between transplant and either death or last follow-up. Progression-free survival (PFS) was defined as the duration of survival after transplant without disease progression, relapse, and death.

End points and statistical analysis

The primary end points were 2-year OS and PFS. The secondary end points included NRM within 100 days and 1-year of transplant, incidence of acute GVHD, and relapse rates. These end points were compared between CST and RIST recipients. For the analysis of OS and PFS, patients were stratified according to the risk of the underlying disease.

OS and PFS were determined using the Kaplan–Meier method. The last follow-up was on 1st August 2003. Median follow-up of surviving patients was 26.6 months (range, 9.5–63.6). Surviving patients were censored on the last day of follow-up. Acute GVHD was analyzed in patients who achieved initial engraftment. Cumulative incidence of acute GVHD, relapse rates, and NRM was calculated using Gray's method, considering each other event as a competing risk.[13]

Clinical characteristics were compared between CST- and RIST recipients using Fisher's exact test or the Mann–Whitney test. A multivariate Cox proportional hazards model was used to identify independent and significant prognostic factors on OS. The variables entered in each analysis were patient age, sex, primary disease, their risks, PS, and type of preparative regimens (CST *vs* RIST). Acute and/or chronic GVHD was included as a time-dependent covariate. A significance level of 5% was set as the limit for inclusion in the model. Prognostic factors, significant at $P<0.05$ in the stepwise proportional model analysis, were considered to be of importance in influencing survival.

Results

Patient characteristics and transplantation procedures

Types of transplants were CST ($n=137$) and RIST ($n=70$). Patient characteristics and transplantation procedures are shown in Table 1. Between the two groups, there were significant differences in age, sex, types of stem cells, presence of infectious complications at transplant, and PS.

Table 1 Characteristics of patients

Variables	*CST (n = 137)*	*RIST (n = 70)*	*P-value*
Pretransplant factors			
Age			
Median (range)	52 (50–59)	57 (50–59)	<0.01*
Sex			
Male/female	93/44	35/35	0.012*
Underlying diseases			
AML	56 (41%)	33 (47%)	0.42
ALL	27 (20%)	8 (11%)	
CML	34 (25%)	16 (23%)	
MDS	20 (15%)	13 (19%)	
Risk of underlying diseases[a]			
Total: low/high	63/74	25/45	0.18
AML: low/high	19/37	7/26	
ALL: low/high	14/13	5/3	
CML: CP/BC/AP	19/3/4	12/3/2	
MDS: RA/RAEB/RAEB in T/CMMoL	0/0/0/1	1/1/1/1	
Stem cells[b]			
Peripheral blood/bone marrow	57/80	68/2	<0.01*
Complications			
Cardiac impairment	5	3	0.72
Liver dysfunction	10	6	0.78
Respiratory dysfunction	6	6	0.22
Infection	9	11	0.028*
Performance status (PS)			
0–1/2–4	123/12	54/13	0.033*
Sex mismatch			
Donor → Recipient; F → M	35	12	0.17
Transplantation procedures			
Conditioning regimen	12 Gy TBI-based	74 (54%)	
BU/CY-based	51 (37%)		
TBI/BU/CY	12 (9%)		
Cladribine-based		6 (9%)	
Fludarabine-based		61 (87%)	
2 GY TBI-based		3 (4%)	
GVHD prophylaxis			
CSP	3 (2%)	32 (46%)	
CSP + sMTX	124 (91%)	23 (33%)	
FK506 + sMTX	5 (4%)	8 (11%)	
Others	5 (4%)	7 (10%)	

*Statistically significant.
[a]We divided the risk of transplantation into two groups. The low-risk group was as follows: acute myeloid or lymphoid leukemia in first remission, chronic myelogeneous leukemia in chronia phase, and myelodysplastic syndrome refractory anemia.
[b]Four patients were infused both peripheral and bone marrow.
CST = conventional stem cell transplantation; RIST = reduced-intensity stem cell transplantation; TBI = total body irradiation; CY = cyclophosphamide; BU = busulfan; 2-CdA = cladribine; Flu = fludarabine; Mel = melpharan; CSP = cyclosporine; sMTX = short-term methotrexate; AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; CML = chronic myelocytic leukemia; MDS = myelodysplastic syndrome; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB in T = refractory anemia with excess blasts in transformation; CMMoL = chronic myelomonocytic leukemia.

RIST recipients had poorer characteristics than CST recipients.

All the CST recipients received either TBI-based or busulfan/cyclophosphamide-based regimens. RIST regimens were purine analog based ($n = 67$), and 2 Gy TBI based ($n = 3$).

Most CST recipients (129/137) received a combination of calcineurin inhibitors (cyclosporin or tacrolimus) and short-term methotrexate as GVHD prophylaxis, while 32 of the 70 RIST received cyclosporin alone as GVHD prophylaxis (Table 1).

Engraftment

Six CST recipients (9%) died of NRM before engraftment. Neutrophils did not decrease below 0.5×10^9/l in 6 RIST recipients (9%). The other 131 CST recipients (96%) and 64 RIST recipients (91%) achieved primary neutrophil engraftment. The median intervals between transplant and neutrophil engraftment were 15 days (range, 5–27) and 12 days (range, 9–30) in CST and RIST, respectively.

Secondary graft failure developed in three patients (CST 2 and RIST 1) 3–9 months after transplant. All the three patients died of infectious complication during neutropenia.

NRM

In all, 23 CST (17%) and five RIST recipients (7%) died of NRM within 100 days of the transplant. Cumulative incidences of 100 days NRM following CST and RIST were 16% (95% confidence interval (CI), 10–22%) and 7% (95% CI, 1–14%), respectively ($P = 0.040$). As of August 2003, 46 CST (34%) and 16 RIST recipients (23%) died of NRM. The median onset of NRM following CST and RIST was day 95.5 (range, 2–967) and day 254 (range, 49–724), respectively. Cumulative incidences of 1-year NRM following CST and RIST were 31% (95% CI, 23–39%) and 15% (95% CI, 6–23%), respectively ($P = 0.0062$, Figure 1). Primary causes of NRM following CST and RIST are

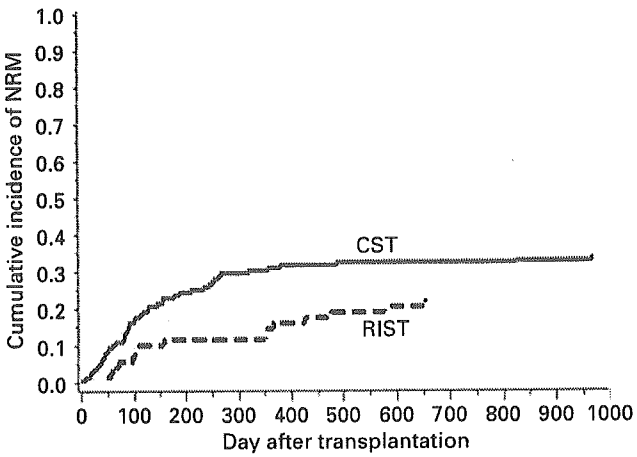

Figure 1 Cumulative incidences of NRM following CST and RIST. Cumulative incidences of NRM following CST and RIST were 31% (95% CI, 23–39%) and 15% (95% CI, 6–23%), respectively.

shown in Table 2. NRM attributable to RRT occurred in 12 and one patient following CST and RIST, respectively.

Graft-versus-host disease

A total of 130 CST and 68 RIST recipients were evaluable. There was no difference in the cumulative incidences of grade II–IV acute GVHD between CST and RIST (Figure 2).

In CST, grade II–IV and grade III–IV acute GVHD occurred in 56 (43%) and 24 patients (18%), respectively. The median onset of grade II–IV acute GVHD was day 23 (range, 3–146 days). GVHD was fatal in 13 of the 56 patients. Of the 104 patients who survived longer than 100 days, 60 patients (58%) developed chronic GVHD.

In RIST, grade II–IV and grade III–IV acute GVHD developed in 38 (56%) and 16 (24%), respectively. The median onset of grade II–IV acute GVHD was day 44 (range, 7–109). GVHD was fatal in 11 of the 38 patients. Of the 57 patients who survived longer than 100 days, 37 (65%) developed chronic GVHD.

Survival

As of August 1, 2003, median follow-ups of surviving patients following CST and RIST were 31.6 months (range, 9.5–63.6) and 20.3 months (range, 9.5–38.4), respectively. Disease-specific outcomes are shown in Table 3.

In all, and low-risk patients, significant differences were not observed in OS between CST and RIST ($P=0.25$, $P=0.69$) (Figures 3 and 4). Among the high-risk patients, there was a significant difference between the two groups ($P=0.044$). The 2-year OS following CST and RIST was 27 and 37%, respectively (Figure 5). There was no significant difference in PFS between CST and RIST among all and low-risk patients ($P=0.39$, $P=0.77$). Among high-risk patients, there was a trend toward better PFS after RIST ($P=0.063$). The 2-year PFS following CST and RIST was 30 and 56%, respectively.

Underlying diseases relapsed in 38 CST and 23 RIST recipients. There was no significant difference in the cumulative incidence of 1-year relapse rates between the two groups; CST 24% (95% CI, 17–32%) and RIST 29% (95% CI, 19–40%) ($P=0.21$, Figure 6).

Risk factors

A univariate analysis revealed that CML ($P<0.0001$), risk of underlying diseases ($P=0.0002$), PS ($P<0.0001$), and

Table 2 Causes of deaths

	CST	*RIST*
Relapse	28	16
Graft-versus-host disease	13	11
Infection	4	0
Bacteria	5	0
Virus	4	1
Fungi		
Idiopathic pulmonary syndrome	5	0
Thrombotic microangiopathy	5	1
Hepatic venoocclusive disease	2	0
Secondary malignancy	2	1
Cardiac failure	1	1
Cerebral infarction	1	0
Others	4	1

CST = conventional stem cell transplantation; RIST = reduced-intensity stem cell transplantation.

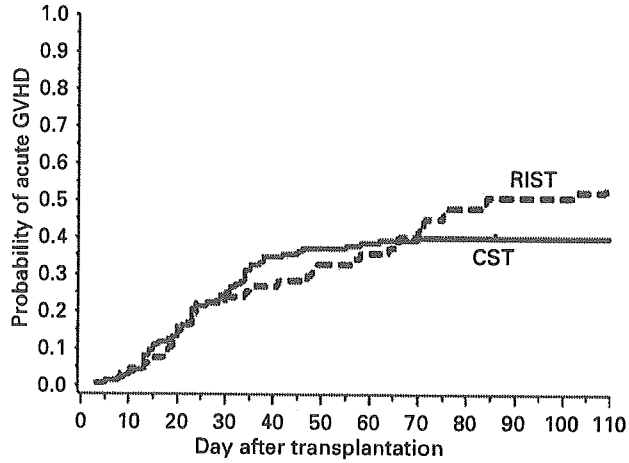

Figure 2 Cumulative incidences of grade II–IV acute GVHD. There was no difference in the cumulative incidences of grades II–IV acute GVHD between CST and RIST.

Table 3 Disease-specific outcomes

Underlying disease	*Type of transplant*	*Number of patients*	*Nmber of patients who died of TRM*	*Number of patients who developed disease progression*	*2-year overall survival*[a]
AML	CST	56	19	20	38.7 (25.8–51.6)
	RIST	33	8	12	69.3 (53.4–85.2)
ALL	CST	27	11	10	33.3 (15.5–51.1)
	RIST	8	2	3	50.0 (15.3–84.7)
MDS	CST	34	8	5	45.0 (23.2–66.8)
	RIST	16	5	3	53.8 (26.8–80.8)
CML	CST	20	8	3	73.4 (58.5–88.3)
	RIST	13	1	5	93.3 (80.8–100)

[a]Each column denotes a rate of 2-year overall survival and its 95% confidence interval.
AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; MDS = myelodysplastic syndrome; CML = chronic myelocytic leukemia; TRM = transplant-related mortality; CST = conventional stem-cell translantation; and RIST = reduced intensity stem cell transplantation.

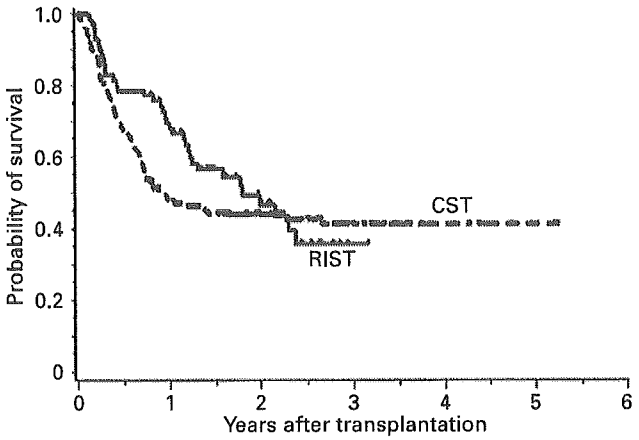

Figure 3 Overall survival (OS) following CST and RIST in all patients. There was no significant difference in OS between CST and RIST ($P=0.25$).

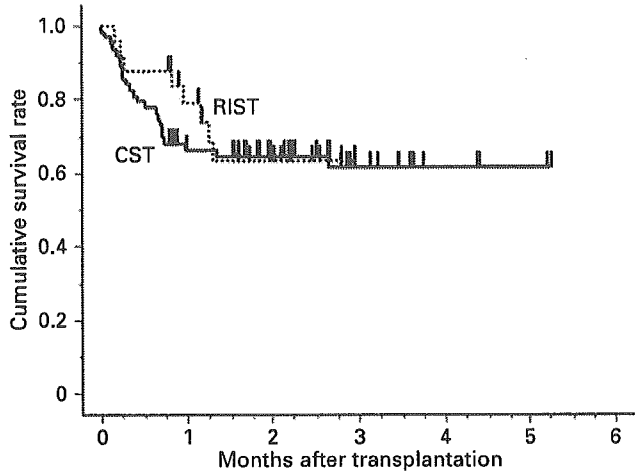

Figure 4 OS following CST and RIST in patients with low-risk diseases. There was no significant difference in OS between CST and RIST ($P=0.69$).

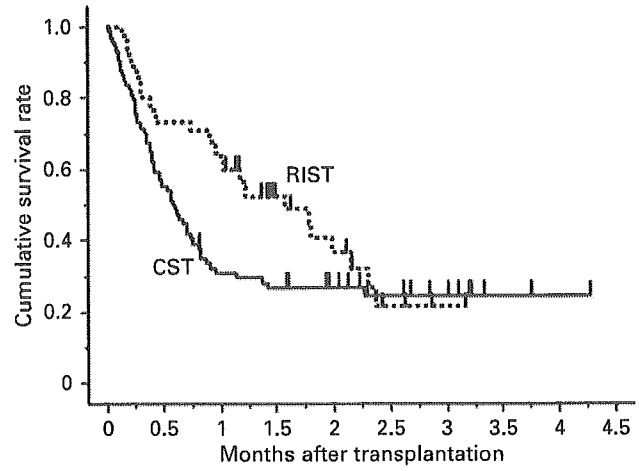

Figure 5 OS following CST and RIST in patients with high-risk diseases. There was a significant difference in OS between CST and RIST ($P=0.044$). The 2-year OS following CST and RIST were 27 and 37%, respectively.

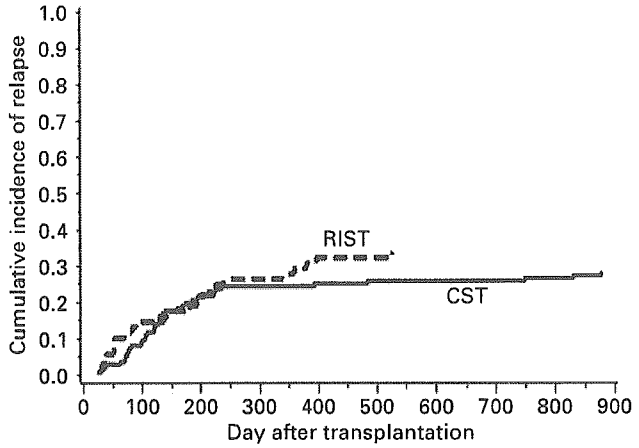

Figure 6 Cumulative incidences of relapse following RIST and CST. There was no significant difference in cumulative incidences of relapse between RIST and CST.

Table 4 Risk factors for overall survival following allogeneic hematopoietic stem-cell tranplantation

	Hazard ratio	*95% confidence interval*	*P-value*
Factors			
Univariate analysis			
Pretransplant factors			
Sex: Female	0.85	0.58–1.25	0.40
Age: 56–59 *vs* 50–51 years	1.11	0.72–1.70	0.63
Donor: female to male recipient	1.22	0.80–1.88	0.35
Disease	1.00		0.0002
CML	0.29	0.15–0.58	
ALL	1.30	0.73–2.31	
AML	0.91	0.55–1.51	
Risk of underlying diseases; high	2.30	1.58–3.37	<0.0001*
PS: 2–4	3.49	2.16–5.64	<0.0001*
Preparative regimen; CST	1.26	0.85–1.88	0.25
Posttransplant factor			
Grade II–IV acute GVHD; presence	2.58	1.76–3.79	<0.0001*
Variables			
Multivariate analysis			
Preparative regimen; CST *vs* RIST	1.92	1.25–2.97	0.003*
PS; 2–4 *vs* 0–1	2.50	1.51–4.16	<0.001
Disease; CML	0.38	0.21–0.69	0.002
Risk of underlying diseases; high	1.85	1.21–2.83	0.004
Grade II–IV acute GVHD; presence	2.57	1.72–3.84	<0.001*

*Statistically significant.
AML = acute myeloid leukemia; CML = chronic myelogeneous leukemia; MDS = myelodysplastic syndrome; ALL = acute lymhoid leukemia; PS = performance status; CST = conventional stem-cell transplantation; GVHD = graft-versus host disease.

development of GVHD ($P<0.001$) were significant risk factors for OS (Table 4). On multivariate analysis, five variables were significant: preparative regimens (CST *vs* RIST) (hazard ratio (HR) = 1.92, 95% CI, 1.25–2.97; $P=0.003$), PS (2–4 *vs* 0–1) (HR = 2.50, 95% CI,

1.51–4.16; $P<0.001$), risk of underlying diseases (HR = 1.85, 95% CI, 1.21–2.83; $P=0.004$), development of grade II–IV acute GVHD (HR = 2.57, 95% CI, 1.72–3.84; $P<0.001$), and CML (HR = 0.38, 95% CI, 0.21–0.69; $P=0.002$).

Discussion

This study suggests that patients with hematologic malignancies aged between 50 and 59 years can achieve remission following RIST as well as CST. There was no significant difference in OS and PFS between RIST and CST (Figure 3). Follow-up of this study was too short to draw a definite conclusion; however, short-term survivals tended to be better in RIST recipients than in CST recipients in the high-risk group (Figure 5). These situations were in contrast to the low-risk group, in which OS and PFS were similar between the two groups (Figure 4). Myeloablative preparative regimens might have been intolerable for high-risk elderly patients. Patients with more progressive diseases might have received CST rather than RIST.

Most physicians believe that it is difficult to control advanced hematologic malignancies with RIST.[5,7] Yet, feasibility of myeloablative preparative regimens has not been fully investigated in patients aged between 50 and 59 years. It is questionable whether intensification of preparative regimens is beneficial for controlling advanced or chemoresistant hematologic malignancies in these patients, because patients with high-risk hematologic malignancies frequently have organ damage due to repeated cytotoxic chemotherapies prior to transplantation.[14] These patients are at high risk of NRM.[15,16] As shown in this study, a myeloablative preparative regimen is not necessarily beneficial in allo-HSCT for elderly patients with high-risk hematologic diseases. In contrast, patients aged between 50 and 59 years in good physical condition are able to tolerate a high-dose preparative regimen. Variables such as CML, low-risk underlying disease, and good PS were independent good prognostic factors for OS. We should tailor preparative regimens considering the patient's condition and risk of the underlying disease.

There are two types of complications associated with allo-HSCT. One is RRT, which often occurs within 30 days of transplantation.[3] The other is GVHD, which is frequently complicated with infections.[14,17] In the present study, there was a significant difference in NRM attributable to RRT between CST and RIST (16 *vs* 7%, $P=0.04$). Reduced-intensity regimens cause less organ damage, contributing to less NRM. These findings were comparable to previous reports.[4,16,18]

GVHD is the most significant concern after allo-HSCT. This study confirmed the previous studies on GVHD following RIST.[19,20] There was no significant difference in the incidence of GVHD between CST and RIST (43 *vs* 56%), and onset of GVHD was delayed in RIST compared with CST. Mortality of GVHD was similar between CST and RIST (23 *vs* 29%). Development of grade II to IV acute GVHD was an independent poor prognostic factor for OS (HR = 2.57, 95% CI, 1.72–3.84; $P<0.001$). These findings demonstrate that GVHD is a significant complication following RIST as well as CST, and that its optimal management awaits further investigation. Balancing GVHD and GVL effects is a delicate issue in allo-HSCT. The augmentation of GVHD prophylaxis may hamper GVL effects, and malignant cells cannot be eradicated by reduced-intensity conditioning alone. Augmentation of GVL effects such as prophylactic donor lymphocyte infusion, vaccination, and administration of cytotoxic T-cells[21] may be beneficial to control residual leukemia without increasing regimen-related mortality. At present, allo-HSCT recipients received uniform GVHD prophylaxis irrespective of the risk of underlying diseases and the patient's condition. In the future, management of GVHD should be optimized considering the risk of the underlying disease and patient conditions.

Relapse is another concern in RIST. This study did not show significant differences in relapse rates between CST and RIST (Figure 6). The unexpectedly low relapse rates following RIST suggest that it has a strong antitumor activity through allogeneic immunity. Augmentation of allogeneic immunity without increasing the intensity of the arative regimen is promising for controlling advanced hematological malignancies. However, late relapse might increase following RIST due to the lack of reduction of leukemic cells by the preparative regimen. It is too early to draw definite conclusions about the incidence of late relapse following RIST based on the results of this study, since allo-HSCT recipients have a considerable risk of relapse within 3 years of transplant[22] and median follow-up of surviving patients was only 26.7 months. Long-term follow-up is required to clarify the prognosis of RIST recipients.

This is a small-sized retrospective study, and we should be careful in interpreting results. The most important was a difference in patient backgrounds between CST and RIST recipients. To minimize unrecognized biases, patients enrolled in this study were limited to those aged between 50 and 59 years who had leukemia or MDS. Yet, RIST recipients were significantly older, and their disease status and PS were significantly worse than CST recipients. These variables influence survival following RIST[7,23] as well as CST.[24–26] Furthermore, there was a wide difference in GVHD prophylaxis between CST and RIST. Most RIST recipients received cyclosporin alone. Short-term methotrexate, and cyclosporin or tacrolimus were given to CST recipients. The median follow-up of surviving patients enrolled in this study was 26.6 months, and thus too short, requiring further observation. Considering these facts, it is difficult to make an accurate comparison between reduced-intensity and myeloablative preparative regimens in this study. We are now planning a prospective randomized study to compare RIST with CST for hematologic malignancies.

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Appendix

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