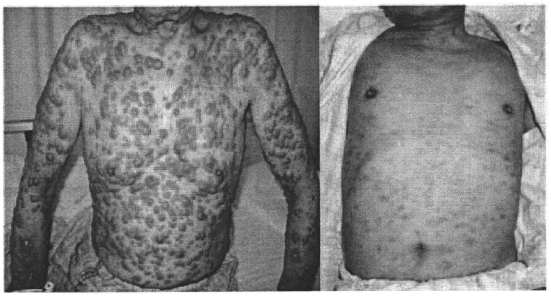

Figure 1 Skin tumors covering whole body of the patient just before RI-UCBT (**a**). Skin tumors of the patient had disappeared in 90 days after RI-UCBT (**b**).

sustained CR so that he had enough time to return to his job. Although CB has been shown to have functionally immature immune cells, it showed its extremely powerful anti-leukemic activity even from the early period post transplant, as the patient's skin lesion had never disappeared during induction chemotherapy including high-dose Ara-C.

Whether the clinical course of this case can be applicable to all aged patients or this is exceptional case needs to be investigated carefully. The indication of allo-SCT for those who are elderly has to be determined individually with extremely careful and repeated discussion with patients, families and transplant staff. Nevertheless, the indication of allo-SCT should not be determined by age as a sole factor. Otherwise, elderly patients may lose chance of cure or good disease control, by not performing toxic yet powerful treatment, such as transplant.

Conflict of interest

The authors declare no conflict of interest.

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CASE REPORT

Monobactam and aminoglycoside combination therapy against metallo-β-lactamase-producing multidrug-resistant Pseudomonas aeruginosa screened using a 'break-point checkerboard plate'

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Abstract

Metallo-β-lactamase-producing multidrug-resistant Pseudomonas aeruginosa (MDR P. aeruginosa) is a cause of life-threatening infections. With parenteral colistin not available in Japan, we treated MDR P. aeruginosa sepsis with monobactam and aminoglycoside combination therapy, with screening using a 'break-point checkerboard plate'.

Introduction

Multidrug-resistant Pseudomonas aeruginosa (MDR P. aeruginosa), defined as P. aeruginosa resistant to aminoglycosides, carbapenems, and fluoroquinolones, has emerged as an increasingly problematic cause of hospital-acquired infection. The outcome of MDR P. aeruginosa sepsis in severely immunocompromised patients is usually poor. With parenteral colistin not available in Japan, effective antimicrobial options are severely limited. Therefore, combination therapy involving available antimicrobial agents is expected. We treated MDR P. aeruginosa sepsis with monobactam and aminoglycoside combination therapy, with screening using a 'break-point checkerboard plate' [1].

Case reports

Patient 1

A 58-y-old woman was admitted to Toranomon Hospital, Tokyo (890 beds) for the treatment of malignant lymphoma. She was treated with an unrelated donor bone marrow transplantation. The patient suffered from grade IV acute graft-versus-host disease (GVHD). On day 74 of transplantation, peritonitis due to perforation was suspected. MDR P. aeruginosa was cultured from the blood, and treatment with intravenous aztreonam (1 g i.v. every 6 h) and amikacin (400 mg i.v. every 24 h) were started according to the break-point checkerboard plate results. The patient subsequently recovered from MDR P. aeruginosa sepsis.

Patient 2

A 54-y-old man was admitted to Toranomon Hospital for the treatment of malignant lymphoma. He received chemotherapy (R-HyperCVAD/MA) and pelvic radiation therapy. He became febrile 9 days after the most recent course of chemotherapy, with a neutrophil count of 176/μl. Treatment with meropenem and vancomycin was ineffective and the high fever persisted. MDR P. aeruginosa was isolated from blood culture, and combination therapy with aztreonam (2 g i.v. every 12 h) and amikacin (400 mg i.v. every 24 h) was selected for MDR P. aeruginosa according to the break-point checkerboard plate results. The patient recovered successfully from MDR P. aeruginosa sepsis.

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Patient 3

A 63-y-old man was admitted to Toranomon Hospital for the treatment of acute myelogenous leukaemia (AML; World Health Organization classification M1). He was treated with cord blood transplantation. The patient developed redness and swelling in the right eyelid on day 1 of transplantation. He became febrile on day 3 of transplantation. On day 5 of transplantation, MDR P. aeruginosa was cultured from the eye discharge, and his neutrophil count was 0/μl. On day 8 of transplantation, MDR P. aeruginosa was cultured from the blood, and treatment with intravenous aztreonam (1 g i.v. every 6 h) and arbekacin (600 mg i.v. every 24 h) was started. The break-point checkerboard plate results suggested synergistic effects of amikacin in combination with aztreonam and piperacillin. The patient subsequently recovered from MDR P. aeruginosa sepsis.

The clinical characteristics of these 3 patients with MDR P. aeruginosa sepsis are shown in Table I.

Discussion

We have reported cases for which monobactams and aminoglycosides were successfully used concomitantly for MDR P. aeruginosa infection. The production of metallo-β-lactamase was demonstrated by the 3 MDR P. aeruginosa strains using the SMA disc method employing sodium mercaptoacetate (SMA), ceftazidime, and imipenem disks (EIKEN CHEMICAL). Pulsed-field gel electrophoresis was also conducted. The strains from patients 1 and 2 were closely related. The strain from patient 3 was different from those of patients 1 and 2 [2]. In Japan, where intravenous colistin cannot be used, combination antimicrobial therapy is expected to be effective for the treatment of MDR P. aeruginosa. A break-point checkerboard plate is used to evaluate the effect of combination therapy in reference to the breakpoint concentration established from the correlation with clinical efficacy, allowing simultaneous evaluation of the effect of combination antimicrobial therapy using 8 clinically important agents (ceftazidime, piperacillin, imipenem, aztreonam, gentamicin, ciprofloxacin, polymyxin B, and rifampicin) on a single plate. In Japan, a break-point checkerboard plate is commercially available as a BC plate 'EIKEN' from EIKEN CHEMICAL, which includes amikacin, meropenem, and colistin instead of gentamicin, imipenem, and polymyxin B.

Most MDR P. aeruginosa patients remain in a carrier state. Usually, MDR P. aeruginosa seldom causes infection. Therefore, no treatment is recommended for carriers. However, MDR P. aeruginosa is associated with a very poor prognosis when it causes infection, particularly sepsis. Thus, when MDR P. aeruginosa is detected in monitoring cultures for immunocompromised patients, it is important to predict the effect of concomitant use on a break-point checkerboard plate to conduct appropriate early antimicrobial therapy for the infection.

In Japan, the production of metallo-β-lactamase is often involved in the high-level resistance of P. aeruginosa. IMP encoded by the bla_{IMP} gene on a plasmid has been reported [3,4]. Effective combinations of antibacterial drugs seem to vary with strains. Strains producing IMP-type metallo-β-lactamase often remain susceptible to monobactams [5]. The concomitant use of monobactams and aminoglycosides seems to be promising. This regimen is considered to provide a promising second drug of choice for patients in whom intravenous colistin cannot be used.

Aminoglycosides for concomitant use with monobactams will be examined in the future. In Japan, a major drug resistance mechanism against aminoglycosides is inactivation of the antibacterial drugs via acetylation, phosphorylation, etc., by aminoglycoside-modifying enzymes produced by resistant bacteria [6,7]. Other known mechanisms include the methylation of 16S rRNA [8] and increased expression of drug-efflux pumps [9]. Arbekacin is characterized by

Table I. Clinical characteristics of patients with multidrug-resistant Pseudomonas aeruginosa sepsis.

Patient	Sex, age	Underlying disease	Predisposing conditions	Neutropenia	Site of infection	Combination selected by BC plate	Treatment	Clinical response
1	Female, 58 y	Malignant lymphoma	U-BMT, GVHD, diarrhoea	No	Blood, peritonitis	AZT/AMK, PIPC/AMK	AZT/AMK	Recovered
2	Male, 54 y	Malignant lymphoma	Chemotherapy, radiation	Yes (176/μl)	Blood, intestinal tract	AZT/AMK	AZT/AMK	Recovered
3	Male, 63 y	AML	CBT	Yes (0/μl)	Blood, eyelid cellulitis	AZT/AMK, PIPC/AMK	AZT/ABK	Recovered

AML, acute myelogenous leukaemia; U-BMT, bone marrow transplantation from an unrelated donor; GVHD, graft-versus-host disease; CBT, cord blood transplantation; BC plate, break-point checkerboard plate; AZT, aztreonam; AMK, amikacin; PIPC, piperacillin; ABK, arbekacin.

the effect against Gram-negative bacilli, including P. aeruginosa, as well as methicillin-resistant Staphylococcus aureus (MRSA) [8,10,11]. Like amikacin, arbekacin is regarded as a strong candidate for concomitant use with monobactams [12].

Declaration of interest: There is no conflict to declare.

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Prophylactic impact of imatinib administration after allogeneic stem cell transplantation on the incidence and severity of chronic graft versus host disease in patients with Philadelphia chromosome-positive leukemia

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Although allogeneic stem cell transplantation (SCT) is a curative treatment for hematological malignancies, chronic graft-versus-host disease (cGVHD), one of the major complications after SCT, impairs the recipient's quality of life. Therefore, the strategy against cGVHD should be improved.

Recently, it has been reported that the fibrotic change in cGVHD is associated with the activation of transforming-growth-factor-β (TGFβ) and platelet-derived-growth-factor receptor (PDGFR) pathways.[1,2] On the other hand, imatinib, a potent tyrosine kinase inhibitor, is known to inhibit the activation of those pathways,[3] and has been investigated for the treatment for steroid-refractory skin cGVHD.[4,5] Although these studies showed that imatinib was effective as salvage treatment for refractory cGVHD, it remains unknown whether the prophylactic imatinib after SCT affects the incidence and severity of cGVHD.

Therefore, we reviewed the clinical records of patients with chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (PhALL) who underwent allogeneic SCT between 1999 and 2009 and survived without relapse for more than 100 days after SCT at eight institutions participating in the Kanto Study Group for Cell Therapy. In all, 76 patients who did not receive imatinib after SCT until hematological relapse or last follow-up were included in the non-imatinib group. Besides, 20 patients who received imatinib for the prevention of leukemia relapse for at least 3 months after transplantation and who experienced no cGVHD before imatinib administration were included in the imatinib group . Patients who received imatinib for less than 3 months were not included. The diagnosis of cGVHD was based on characteristic manifestations and/or pathological findings.[6] The severity of cGVHD was classified according to the traditional Seattle criteria.[7] In addition, the severity score according to the National Institute of Health Consensus recommendations was also used for the comparison of the severity in each target organ between the two groups, including skin, eye and oral (sicca syndrome), liver, lung, gut, and others, although there was a difficulty in retrospective grading.[6] This analysis was approved by the institutional review board of Jichi Medical University.

The imatinib group included 2 and 18 patients with CML and PhALL, respectively. The non-imatinib group included 43 and 33 patients with CML and PhALL, respectively. Besides, 1 and 33 CML patients were in chronic phase and 17 and 30 PhALL patients were in 1st complete remission in the imatinib and non-imatinib groups, respectively. The proportion of patients with PhALL was significantly higher in the imatinib group ($P=0.0003$). Although more patients in the imatinib group underwent SCT from an alternative donor (14 and 43 patients in the imatinib and non-imatinib group, respectively, $P=0.017$) and received tacrolimus-based GVHD prophylaxis (14 and 30 patients in the imatinib and non-imatinib group, respectively, $P=0.0099$), there was no difference in the incidence of grade 2–4 acute GVHD (Table 1). None received anti-thymocyte globulin-containing conditioning nor T cell depleted graft.

All 20 patients in the imatinib group received imatinib after SCT, but nilotinib or dasatinib was substituted for imatinib in 2 patients at 5 and 12 months after SCT, respectively. The median starting doses of imatinib, nilotinib, and dasatinib were 400 mg (range 100–600), 800 mg, and 70 mg, respectively. The median duration between SCT and the start of imatinib was

Table 1 Patient characteristics

	Total	*Imatinib*	*Non-imatinib*	*P-value*
Sex				
Male	58	11	47	
Female	38	9	29	0.61
Age				
Median (years old)	40	39.5	40	
Range	(16–62)	(18–61)	(16–62)	0.9
Disease				
PhALL	51	18	33	
CML	45	2	43	*0.0003
Imatinib before SCT				
–	33	2	31	
+	63	18	45	*0.0091
Conditioning				
CY/TBI	75	16	59	
CY/BU	5	0	5	
RIC	16	4	12	0.47
Donor source				
MRD	39	6	33	
MMRD	4	0	4	
MUD	38	6	32	
MMUD	6	3	3	
CB	9	5	4	*0.017
Sex-matching				
Match	56	10	46	
M→F	22	7	15	
F→M	18	3	15	0.35
ABO-matching				
Match	47	7	40	
Major mismatch	15	4	11	
Minor mismatch	25	8	17	
Major/minor mismatch	6	1	5	0.4
GVHD prophylaxis				
CsA-based	51		46	5
FK-based	44	14	30	*0.0099
GVHD Grade2–4				
–	62	13	49	
+	34	7	27	>0.99

Abbreviations: BU, busulfan; CB, cord blood; CML, chronic myeloid leukemia; CsA, cyclosporine; CY, cyclophosphamide; Donor sex → recipient sex; FK, tacrolimus; GVHD, graft-versus-host disease; MMUD, mismatched unrelated donor; MMRD, mismatched related donor; MRD, matched related donor; MUD, matched unrelated donor; PhALL, Philadelphia positive acute lymphoblastic leukemia; RIC, reduced-intensity conditioning; SCT, stem cell transplantation.
*P-value <0.05 was considered significant.

65 days (range 13–219 days). Imatinib was started within 100 days after SCT in 16 of the 20 patients (in 18 patients within 120 days after SCT). The median duration of imatinib administration was 170 days (range 115–1284 days). The reasons for the administration of imatinib included planned administration in 14, molecular relapse or minimal residual disease in 5 patients, and isolated central nervous system relapse after SCT in 1 patient.

In total, 62 patients experienced cGVHD. The 3-year cumulative incidence of cGVHD and extensive cGVHD was 41.1 and 22.0%, respectively, in the imatinib group, and 71.3 and 53.0%, respectively, in the non-imatinib groups ($P=0.0083$ and $P=0.0072$) (Figure 1a and b). The details of clinical features of cGVHD symptoms are shown in Table 2. Sicca syndrome ($P=0.047$) and gut involvement ($P=0.036$) were observed less frequently in the imatinib group. The incidences of skin and lung cGVHD were also lower in the imatinib group, but these differences were not statistically significant. No lung involvement was observed during imatinib administration. The severity score of cGVHD was also significantly lower in the imatinib group in sicca syndrome ($P=0.038$) and gut involvement ($P=0.038$). The severity in skin involvement was also lower during imatinib administration in the imatinib group. Finally, the overall severity of cGVHD through the clinical course was significantly lower in the imatinib group ($P=0.029$).

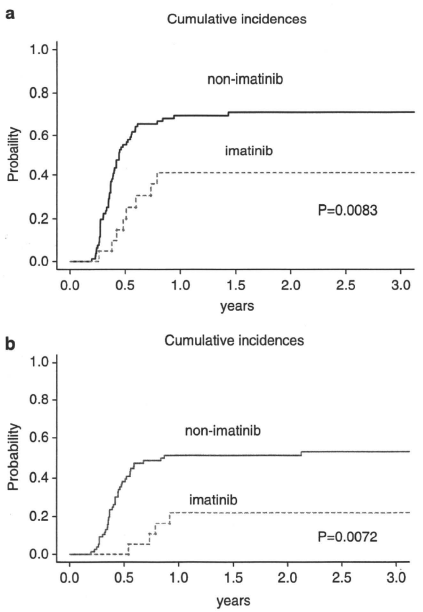

Figure 1 Cumulative incidences of chronic GVHD (**a**) and extensive chronic GVHD (**b**) grouped according to the use of imatinib after stem cell transplantation.

Multivariate analysis revealed that cord-blood transplantation (relative risk (RR) = 0.129, $P=0.045$) and the administration of post-SCT imatinib as a time-dependent covariate (RR = 0.266, $P=0.013$) were the significant independent predictive factors for a lower incidence of cGVHD. Younger age (RR = 1.035, $P=0.011$) and post-SCT imatinib administration (RR = 0.252, $P=0.0087$) were significant for lower incidence of extensive cGVHD (Table 3). GVHD prophylaxis and imatinib administration before SCT did not affect the incidence of cGVHD. The very small number of CML cases in the imatinib group might have resulted in the finding that the diagnosis of CML, which previously was reported as a risk factor for cGVHD, did not remain significant in multivariate analysis.

TGFβ and PDGF are thought to have a role in the pathogenesis of fibrosis. Imatinib inhibits intracellular signaling of these fibrotic cytokines.[3] Although imatinib was recently reported to be a promising salvage treatment for refractory cGVHD,[4,5] this study showed for the first time that imatinib may also be effective as prophylaxis for cGVHD. This might be the reason why no cGVHD was observed in a post-SCT imatinib trial for prevention of disease progression.[8]

Table 2 Details of chronic GVHD

	Imatinib	*Non-imatinib*	*P-value*
Incidence of cGVHD			
Total (%)	8 (40%)	54 (71%)	*0.017
During imatinib (%)	4 (20%)	—	
Incidence of Extensive cGVHD			
Total (%)	4 (20%)	40 (53%)	*0.0011
During imatinib administration (%)	0 (0%)	—	
Type of cGVHD			
De novo	2 (10%)	21 (28%)	
Quiescent	6 (30%)	22 (29%)	
Progressive	0 (0%)	11 (14%)	
None	12 (60%)	22 (29%)	*0.026
Target organs and their severity			
Skin			
Incidence	4 (20%)	25 (33%)	0.29
Score range	[0–1]	[0–3]	0.15
Sicca			
Incidence	5 (25%)	38 (50%)	*0.047
Score range	[0–2]	[0–3]	*0.038
Liver			
Incidence	5 (25%)	35 (46%)	0.13
Score range	[0–3]	[0–3]	0.12
Lung			
Incidence	1 (5%)	8 (11%)	0.68
Score range	[0–2]	[0–3]	0.43
Gut			
Incidence	0	14 (18%)	*0.036
Score range	[0–0]	[0–3]	*0.038
Others			
Incidence	0	6 (8%)	0.34
Score range	[0–0]	[0–2]	0.19
Overall severity			
None (=0)	12 (60%)	23 (30%)	
Mild (=1)	3 (15%)	19 (25%)	
Moderate (=2)	3 (15%)	19 (25%)	
Severe (=3)	2 (10%)	15 (20%)	*0.029

Abbreviations: GVHD, graft-versus-host disease; SCT, stem cell transplantation.
*P-value <0.05 was considered significant.

Table 3 Predictive factors for the incidence of chronic GVHD

	Univariate analysis			*Multivariate analysis*		
	RR	*95% CI*	*P-value*	*RR*	*95% CI*	*P-value*
Chronic GVHD						
Imatinib after SCT	0.235	(0.085–0.65)	0.0052	0.266	(0.0935–0.757)	*0.013
Donor source						
MRD	1			1		
MMRD	0.63	(0.150–2.65)	0.53	0.573	(0.136–2.409)	0.45
MUD	1.2	(0.712–2.034)	0.49	1.314	(0.776–2.225)	0.31
MMUD	0.632	(0.192–2.08)	0.45	1.046	(0.308–3.555)	0.94
CB	0.097	(0.0131–0.714)	0.022	0.129	(0.0174–0.953)	*0.045
Age	1.02	(0.998–1.043)	0.073	—		
Conditioning						
CY/TBI	0.548	(0.299–1.003)	0.051	—		
BU/CY	1.128	(0.368–3.451)	0.83	—		
RIC	1			—		
Presence of acute GVHD	1.618	(0.9737–2.688)	0.063	—		
Extensive cGVHD						
Imatinib after SCT	0.268	(0.0958–0.751)	0.0122	0.252	(0.0897–0.706)	*0.0087
Age	1.032	(1.005–1.060)	0.019	1.035	(1.008–1.063)	*0.011
Disease						
CML	1.854	(1.015–3.385)	0.044	—		
PhALL	1			—		
Conditioning						
CY/TBI	0.48	(0.245–0.941)	0.033	—		
BU/CY	0.59	(0.132–2.643)	0.49	—		
RIC	1			—		

Abbreviations: BU, busulfan; CB, cord blood; CI, confidence interval; CML, chronic myeloid leukemia; CY, cyclophosphamide; GVHD, graft-versus-host disease; MMUD, mismatched unrelated donor; MMRD, mismatched related donor; MRD, matched related donor; MUD, matched unrelated donor; PhALL, Philadelphia positive acute lymphoblastic leukemia; RIC, reduced-intensity conditioning; RR, relative risk; SCT, stem cell transplantation.
*P-value <0.05 was considered significant.

Based on reports of imatinib as an inhibitor of TGFβ and PDGFR,[3] we had initially predicted that imatinib might strongly affect skin and lung involvement. In fact, the incidences of skin and lung cGVHD were reduced in the imatinib group, although the difference was not statistically significant. In addition, when we focused on the severity only during imatinib administration, the severity in skin involvement was lower and no lung involvement was observed in the imatinib group. Furthermore, a deterioration of sclerotic cGVHD was observed after the discontinuation of imatinib in four patients. These findings suggest that sclerotic involvement might be inhibited mainly during imatinib administration through the inhibition of TGFβ or PDGF. In this study, however, prophylactic imatinib administration appeared mainly to reduce the incidence and severity of sicca and gut involvement. Although the actual mechanism is unclear, suppression of mast-cell activation in intestinal mucosa and salivary glands by inhibition of the c-kit pathway by imatinib might have been involved as well, similar to Sjogren's disease and inflammatory bowel diseases.[9,10] In addition, imatinib inhibits T-cell proliferation *in vitro*.[11] Therefore, imatinib might prevent cGVHD through a direct immunosuppressive effect.

In summary, the incidence and severity of cGVHD were reduced by imatinib administration after SCT. However, this study has limitations because of its retrospective nature. A large prospective study is warranted to assess the prophylactic impact of imatinib on the incidences of leukemia relapse and cGVHD after allogeneic SCT for PhALL and CML.

Conlfict of interest

The authors declare no conflict of interest.

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Gene expression analysis reveals *HOX* gene upregulation in trisomy 8 AML

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Acute myeloid leukemia (AML) is a heterogeneous disease. Among chromosomal numerical aberrations, trisomy 8 (+8) is the most common chromosomal change, conferring an intermediate prognosis, and is associated with the t(7;12), t(9;11) and t(1;11) translocations.[1] Alone, trisomy 8 does not appear to be sufficient for leukemogenesis but may be associated with an increased risk of myeloid malignancy.[1] To investigate further the contribution of +8 to AML, we determined the gene expression signature associated specifically with this numerical chromosomal abnormality using large, previously reported, AML microarray data sets[2,3] and data sets derived from AML cell lines. We have identified a novel association between *HOXA* gene upregulation and +8 AML providing new insight into the potential contribution of +8 to AML pathogenesis.

We first analyzed the large AML microarray data set (Affymetrix HGU133A, Santa Clara, CA, USA) from the study by Valk *et al.*[2] (GSE1159). Criteria for inclusion were patients with a +8 karyotype without any other karyotypic abnormalities, such as translocations, or other numerical chromosomal aberrations. Patients with a +8 karyotype and mutations in *FLT3*, *EVI1*, *RAS*, *CEBPA* or *NPM1* genes were not excluded. Data were normalized with Robust Multichip Average (RMA) and the gene expression change for each gene determined in the +8 AML group ($n=16$), relative to the expression level in normal bone marrow mononuclear cells (NBM, $n=5$). This approach focused on genes in the selected AML group that may contribute to the leukemic phenotype by virtue of their association with the block in differentiation, increased self-renewal, increased survival and proliferative potential. To generate the final +8 AML gene set, we selected genes that are selectively differentially expressed in +8 AML compared to NBM but not differentially expressed in the other common AML numerical chromosome abnormalities, monosomy 7 (−7) and −7q. Analysis was performed using linear modeling analysis package available from the Bioconductor (http://www.bioconductor.org/). Genes with multiple probes were filtered based on an adjusted false discovery rate *P*-value controlled using Benjamini–Hochberg method. The analysis was performed using R (http://www.r-project.org/). This approach identified 90 genes (false discovery rate *P*-value <0.01) that display selective differential gene expression in AML associated with trisomy 8 (Figure 1). The top 10 up- and downregulated genes ranked based on fold change are shown in Table 1.

Seven of the differentially regulated genes were located on chromosome 8 (marked with a double asterisk in Figure 1) and, as may be predicted from the +8 genotype and shown by previous gene expression studies (reviewed by Paulsson and Johansson[1]), the expression of six of these was upregulated. Unsupervised clustering with MeV (http://www.tm4.org/mev/) using the +8 AML gene signature showed that +8 AML clustered together with the mixed-lineage leukemia (MLL) translocation group and with normal karyotype AML (Figure 1) This is in line with the clinical findings that +8, MLL and normal karyotype AML form a well-defined prognostic group (G1) with intermediate outcome[4] (Figure 1). Of significant interest, we identified several *HOX* genes (*HOXA9*, *HOXA10* and *HOXA1*) that display increased expression in the +8 AML group relative to most other karyotypic groups and NBM (Figure 2). Several *HOX* genes from the *HOXA* cluster, in particular *HOXA9*, have important roles in hematopoiesis and leukemogenesis.[5] This is the first report of increased *HOX* gene expression as a feature of +8 AML, although increased *HOX* gene expression has been reported in AML with MLL rearrange-

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ORIGINAL ARTICLE

A decision analysis of allogeneic hematopoietic stem cell transplantation in adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission who have an HLA-matched sibling donor

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Clinical studies using genetic randomization cannot accurately answer whether adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) who have a human leukocyte antigen (HLA)-matched sibling should undergo allogeneic hematopoietic stem cell transplantation (HSCT) or chemotherapy in first remission, as, in these studies, patients without a sibling donor undergo alternative donor transplantation or chemotherapy alone after a relapse. Therefore, we performed a decision analysis to identify the optimal strategy in this setting. Transition probabilities and utilities were estimated from prospective studies of the Japan Adult Leukemia Study Group, the database of the Japan Society for Hematopoietic Cell Transplantation and the literature. The primary outcome measure was the 10-year survival probability with or without quality of life (QOL) adjustments. Subgroup analyses were performed according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification. In analyses without QOL adjustments, allogeneic HSCT in first remission was superior in the whole population (48.3 vs 32.6%) and in all subgroups. With QOL adjustments, a similar tendency was conserved (44.9 vs 31.7% in the whole population). To improve the probability of long-term survival, allogeneic HSCT in first remission is recommended for patients who have an HLA-matched sibling.
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Introduction

With modern intensive chemotherapy, 74–93% of adult patients with acute lymphoblastic leukemia (ALL) achieve complete remission. However, the overall survival rate is only 27–48% because of the high rate of relapse.[1] Therefore, the establishment of optimal postremission therapy is important. The efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) for adult patients with ALL in first remission has been demonstrated through clinical studies using genetic randomization, in which patients with a human leukocyte antigen (HLA)-matched sibling donor were allocated to the allogeneic HSCT arm, and those without a donor were placed in the chemotherapy or autologous transplantation arm. First, the LALA-87 trial showed that overall survival in patients with a donor was better than that in patients without a donor in a subgroup analysis of patients with high-risk characteristics.[2] A meta-analysis of seven similar studies confirmed that the donor group was superior to the non-donor group in patients with high-risk ALL in first remission.[3] However, such genetic randomization studies cannot accurately answer the question of whether patients with an HLA-matched sibling should undergo allogeneic HSCT or chemotherapy in first remission. In these studies, patients without a sibling donor had to choose transplantation from an alternative donor or chemotherapy alone once they had a relapse. The outcome of these treatments has been reported to be inferior to that of HSCT from an HLA-matched sibling donor in patients with relapsed ALL; therefore, the expected survival after the decision to continue chemotherapy in first remission in patients without a sibling donor is assumed to be originally poorer than that in patients with a sibling donor. However, it is practically difficult to perform a clinical trial in which patients with an HLA-matched sibling in first remission are randomly assigned to receive allogeneic HSCT or chemotherapy alone. Another important problem has been poor compliance with the assigned treatment in some studies. In addition, previous genetic

randomization studies did not consider the quality of life (QOL), especially that associated with graft-versus-host disease (GVHD). Therefore, we performed a decision analysis incorporating QOL adjustments using a decision tree based on the results of Japan Adult Leukemia Study Group (JALSG) prospective studies (ALL93[4] and ALL97[5]), the database of the Japan Society for Hematopoietic Cell Transplantation (JSHCT)[6] and literature. Patients with Philadelphia chromosome (Ph)-positive ALL were not included in our analysis because the outcome of treatment in these patients has improved dramatically since tyrosine kinase inhibitors became available.[7]

Recently, the Medical Research Council/Eastern Cooperative Oncology Group (MRC/ECOG) trial demonstrated the efficacy of allogeneic HSCT in ALL patients and in standard-risk patients, but not in high-risk patients,[8] which was inconsistent with previous studies. This difference might partly depend on the definition of high-risk patients. In the MRC/ECOG study, an age of higher than 35 years was considered to be a high-risk factor. Therefore, we performed separate subgroup analyses according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification with a cutoff of 35 years.

Methods

Model structure

We constructed a decision tree (Figure 1) to identify the optimal treatment strategy for adult patients with Ph-negative ALL in first remission who have an HLA-matched sibling.[9,10] The square at the left represents a decision node. We can decide to either proceed to allogeneic HSCT or continue chemotherapy in first remission. We did not include a decision to perform autologous HSCT, as autologous HSCT has not been shown to be superior to chemotherapy alone in a meta-analysis.[3] Circles, called chance nodes, follow each decision, and each chance node has two or three possible outcomes with a specific probability called the transition probability (TP). Every branch finally ends with triangles, called terminal nodes, and each terminal node has an assigned payoff value, called utility, according to different health states. Calculations were performed backward, from right to left in the decision tree. The sum of the products of TPs and utilities of the branches becomes the expected value for each chance node, and eventually the sum of the expected values in all of the chance nodes following the decision nodes becomes the expected value of each decision. The following analyses were performed using TreeAge Pro 2009 software (Williamstown, MA, USA). This study was approved by the Committee for Nationwide Survey Data Management of JSHCT, and the Institutional Review Board of Jichi Medical University.

Data sources

Outcomes after continuing chemotherapy in first remission were estimated from JASLG studies (ALL93 and ALL97). Patients with Ph-negative ALL, aged 15–54 years, were included, and those who never achieved remission with chemotherapy were excluded. Data from 122 patients in ALL93 and 119 patients from ALL97 were analyzed separately, and then combined by weighting the number of patients. Outcomes after allogeneic HSCT in various disease statuses were estimated from the database of the JSHCT. Patients with Ph-negative ALL, aged 16–54 years, who underwent a first myeloablative allogeneic HSCT from a serologically HLA-A, -B, -DR loci-matched sibling between 1993 and 2007 were included. Of them, 408, 61, 14 and 94 patients were in first remission, second remission, third or later remission and non-remission, respectively, at allogeneic HSCT.

The characteristics of the patients included in this study are summarized in Table 1. There was no significant difference in their baseline characteristics. To determine the following TPs,

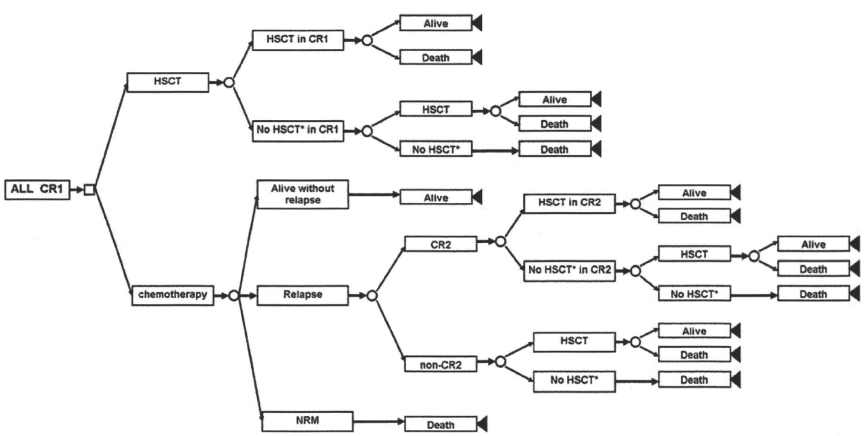

Figure 1 Decision tree used in this study. Decision analysis was performed on the basis of a decision tree. A square indicates a decision node and open circles indicate chance nodes. In analyses with a QOL adjustment, 'Alive' after transplantation was followed by two branches with or without active chronic GVHD. *HSCT was not performed because of early relapse, death and so on. ALL, acute lymphoblastic leukemia; CR, complete remission; NRM, non-relapse mortality.

Table 1 Patient characteristics in the three data sources

	Chemotherapy in CR1		*HSCT in CR1*	P[a]
	JALSG ALL93	*JALSG ALL97*	*JSHCT*	
No. of patients	122	119	408	
Median age (range)	26 (15–54)	26 (15–54)	29 (16–54)	0.72
No. of males/females	72/50	54/65	230/178	0.06
Median WBC count at diagnosis (range) ($\times 10^9$/l)	9.5 (0.6–468.0)	10.2 (0.3–398.0)	10.4 (0.4–801.0)	0.91
Karyotype standard:high[b], ratio	20:1	30:1	15.4:1	0.55

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplantation; JALSG, Japan Adult Leukemia Study Group; JSHCT, Japan Society for Hematopoietic Cell Transplantation; WBC, white blood cell.
[a]Statistical analyses were performed using the Kruskal–Wallis test for continuous variables and the χ^2-test for categorical variables.
[b]t(4;11) and t(1;19) were classified as high-risk karyotypes, and other karyotypes were classified as standard risk.

overall survival and leukemia-free survival (LFS) with a 95% confidence interval (CI) were calculated using the Kaplan–Meier method, whereas the cumulative incidences of non-relapse mortality and relapse with 95% CI were calculated using Gray's method,[11] considering each other as a competing risk. Probabilities that we could not estimate from these data were estimated from the literature.

Transition probabilities (TPs) and utilities

TPs of the whole population were determined as summarized in Table 2. Each TP has a baseline value and a plausible range. Baseline decision analyses were performed on the basis of baseline values.

Patients may have been precluded from undergoing allogeneic HSCT because of early relapse or comorbidities even if they decided to undergo allogeneic HSCT, and therefore the TP of actually undergoing allogeneic HSCT in first remission after the decision branch to undergo allogeneic HSCT was determined as follows: first, the median duration between the achievement of first remission and HSCT without relapse was calculated as 152 days on the basis of JSHCT data. Next, LFS rates at 152 days after achieving first remission were calculated using the data of all patients who achieved remission in the JALSG studies, and the combined LFS was 0.80 (95% CI: 0.76–0.85). We considered this to be the TP for actually receiving HSCT in first remission, and assigned a baseline value of 0.80 and 95% CI to the plausible range. Similarly, patients may be precluded from undergoing allogeneic HSCT even though they have achieved second remission after they had a relapse of leukemia following a decision to continue chemotherapy. This TP of undergoing allogeneic HSCT in second remission could not be calculated from our data. We assigned a plausible range of 0.5–0.80; the former value was the only available rate in a large study[12] and the latter was the TP calculated above. The median of this range was taken as the baseline value. Probabilities regarding the actual rate of receiving HSCT in other disease statuses could not be obtained, even in the literature. Therefore, a baseline value of 0.5 was assigned with a wide plausible range of 0.3–0.7, although these values may not be closely related to the final expected value, as the probability of survival after receiving HSCT in these situations was extremely low. The TPs of 'Alive at 10 years' following HSCT in various disease statuses were determined on the basis of the JSHCT database. We assigned 95% CI to the plausible ranges.

The TPs of 'Alive without relapse at 10 years' and non-relapse mortality following chemotherapy in first remission were determined on the basis of JALSG studies, and the TP of relapse following chemotherapy was determined by subtracting the sum of these TPs from 1. The TP of achieving second remission after relapse in patients who decided not to undergo allogeneic HSCT in first remission was estimated to have a baseline value of 0.4, with a plausible range of 0.3–0.5 based on the literature.[12–14]

The primary outcome measure was the 10-year survival probability as described in the Discussion. The survival curve nearly reaches a plateau after 5 years and therefore 'Alive at 10 years' reflects 'Cure of leukemia', which is the primary goal of allogeneic HSCT. First, we considered only two kinds of health states, 'Alive at 10 years' and 'Dead', and assigned utility values of 100 to the former and 0 to the latter without considering QOL. Next, we performed a decision analysis while adjusting for QOL. 'Alive after chemotherapy without relapse at 10 years', 'Alive with active GVHD at 10 years' and 'Alive without active GVHD at 10 years' were considered as different health states. The proportion of patients with active GVHD among those who

Table 2 Transition probabilities of the whole population

	Baseline value (plausible range)
HSCT in CR1	0.80 (0.76–0.85)
Alive at 10 years following HSCT in CR1	0.57 (0.52–0.63)
HSCT after failure of HSCT in CR1	0.5 (0.3–0.7)
Alive at 10 years following HSCT after failure of HSCT in CR1[a]	0.27 (0.16–0.38)
Alive at 10 years without relapse following CTx	0.21 (0.15–0.28)
NRM at 10 years following CTx	0.07 (0.04–0.10)
Achievement of CR2 after relapse following CTx	0.4 (0.3–0.5)
HSCT in CR2	0.66 (0.5–0.80)
Alive at 10 years following HSCT in CR2	0.38 (0.27–0.53)
HSCT after failure of HSCT in CR2	0.5 (0.3–0.7)
Alive at 10 years following HSCT after failure of HSCT in CR2[b]	0.18 (0.16–0.2)
HSCT in non-CR after relapse following CTx	0.5 (0.3–0.7)
Alive at 10 years following HSCT in non-CR after relapse	0.16 (0.1–0.27)
Rate of active GVHD at 10 years[c]	0.18 (0.1–0.25)

Abbreviations: CR, complete remission; CTx, chemotherapy; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality.
[a]This rate was estimated from the survival rate following HSCT in CR2 and HSCT in non-CR.
[b]This rate was estimated from the survival rate following HSCT in CR3 or more and HSCT in non-CR.
[c]The same baseline value and plausible range were used as the rate of active GVHD at 10 years following HSCT in various disease statuses, but one-way sensitivity analyses were performed separately in each status.

Table 3 Transition probabilities of subgroups

	Baseline value (plausible range)			
	Standard-risk	*High-risk*	*Lower age*	*Higher age*
HSCT in CR1	0.86 (0.81–0.92)	0.65 (0.54–0.77)	0.81 (0.76–0.86)	0.80 (0.72–0.87)
Alive at 10 years following HSCT in CR1	0.6 (0.53–0.68)	0.51 (0.4–0.66)	0.62 (0.55–0.69)	0.48 (0.39–0.58)
Alive at 10 years following HSCT after failure of HSCT in CR1	0.31 (0.24–0.38)	0.28 (0.13–0.43)	0.3 (0.21–0.39)	0.23 (0.11–0.35)
Alive at 10 years without relapse following CTx	0.27 (0.18–0.37)	0.13 (0.03–0.22)	0.19 (0.11–0.27)	0.25 (0.16–0.35)
NRM at 10 years following CTx	0.06 (0.02–0.11)	0.07 (0–0.14)	0.04 (0.01–0.08)	0.11 (0.05–0.18)
HSCT in CR2	0.68 (0.5–0.86)	0.58 (0.5–0.65)	0.66 (0.5–0.81)	0.65 (0.5–0.80)
Alive at 10 years following HSCT in CR2	0.38 (0.23–0.61)	0.43 (0.22–0.84)	0.39 (0.26–0.58)	0.35 (0.19–0.64)
Alive at 10 years following HSCT after failure of HSCT in CR2[a]	0.24 (0.12–0.45)	0.13 (0.05–0.35)	0.21 (0.12–0.36)	0.11 (0.04–0.3)
Alive at 10 years following HSCT in non-CR after relapse	0.24 (0.12–0.45)	0.13 (0.05–0.35)	0.21 (0.12–0.36)	0.11 (0.04–0.3)

Abbreviations: CR, complete remission; CTx, chemotherapy; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality.
Transition probabilities that are not in Table 3 are the same as those mentioned in the whole population.
[a]As the number of patients who underwent HSCT in CR3 or more was not enough, the same rate of survival following HSCT in non-CR was used.

were alive at 10 years was determined on the basis of the literature.[15–17] We assigned a value of 100 to the utility for being alive without relapse at 10 years after chemotherapy alone, and a value of 0 to the utility for being dead in all situations. We assigned a fixed value of 98 to the utility for being alive without active GVHD at 10 years following HSCT, and assigned a value of 70 with a wide plausible range of 0–98 to the utility for being alive with active GVHD at 10 years. These utilities were determined on the basis of opinions of 10 doctors who were familiar with HSCT and the literature.[9,18]

Subgroup analyses were also performed according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification with a cutoff of 35 years. Patients with a high white blood cell count (more than 30×10^9/l for B lineage and more than 100×10^9/l for T lineage) and/or with t(4;11) or t(1;19) were classified as a high-risk group, and all other patients were classified as standard-risk group. All TPs, based on the JALSG studies and the JSHCT data, were recalculated using the data of patients in each subgroup (Table 3). Other TPs and utilities were the same as those for the overall patient analyses.

Sensitivity analyses

To evaluate the robustness of the decision model, we performed one-way sensitivity analyses for all TPs, in which the decision tree was recalculated by varying each TP value in its plausible range, and confirmed whether the decision of the baseline analyses changed. In the analyses that included adjustments for QOL, the utility for being alive with active GVHD at 10 years was also subjected to a one-way sensitivity analysis.

We also performed a probabilistic sensitivity analysis using Monte Carlo simulation in which the uncertainties of all TPs were considered simultaneously.[19] The distribution of the random variables for each TP was determined to follow a normal distribution, with 95% of the random variables included in the plausible range. Following 1000 simulations based on the decision tree, the mean and s.d. of the expected value for each decision were calculated.

Results

Baseline analysis

The baseline analysis in the whole population without adjusting for QOL revealed an expected 10-year survival of 48.3% for the decision to perform allogeneic HSCT in first remission, which was better than that of 32.6% for the decision to continue chemotherapy. The decision to perform allogeneic HSCT continued to be superior even after adjusting for QOL (44.9% for HSCT vs 31.7% for chemotherapy, Table 4).

Table 4 Expected 10-year survival probabilities with and without adjusting for QOL

	Expected survival probability without a QOL adjustment		*Expected survival probability with a QOL adjustment*	
	HSCT (%)	*Chemotherapy (%)*	*HSCT (%)*	*Chemotherapy (%)*
All patients	48.3	32.6	44.9	31.7
Standard-risk patients	53.8	39.8	50.0	38.9
High-risk patients	38.0	25.0	35.4	24.1
Lower-aged patients[a]	53.1	32.9	49.3	31.9
Higher-aged patients[a]	40.7	33.4	37.8	32.8

Abbreviation: HSCT, hematopoietic stem cell transplantation; QOL, quality of life
[a]Lower-aged patients include those aged 35 years or younger. Higher-aged patients include those aged older than 35 years.

Sensitivity analysis

First, we performed one-way sensitivity analyses for all TPs in the decision model without adjusting for QOL. A better expected survival for the decision to perform HSCT was consistently demonstrated in all TPs within the plausible ranges. In the probabilistic sensitivity analysis, the mean value and s.d. of the expected survival probability for HSCT were 48.3 and 2.6%, and those for chemotherapy were 32.7 and 3.4%, respectively.

Next, we performed one-way sensitivity analyses for all TPs and for the utility for being alive with active GVHD at 10 years in the decision model adjusted for QOL. Even in these analyses, the result of the baseline analysis did not reverse in all TPs. In addition, a higher expected survival probability for HSCT was retained, assuming that the utility for being alive with active GVHD ranged between 0 and 98 (Figure 2a). In the probabilistic sensitivity analysis, the mean value and s.d. of the expected survival probability for HSCT were 44.8 and 2.6%, and those for chemotherapy were 31.8 and 3.4%, respectively.

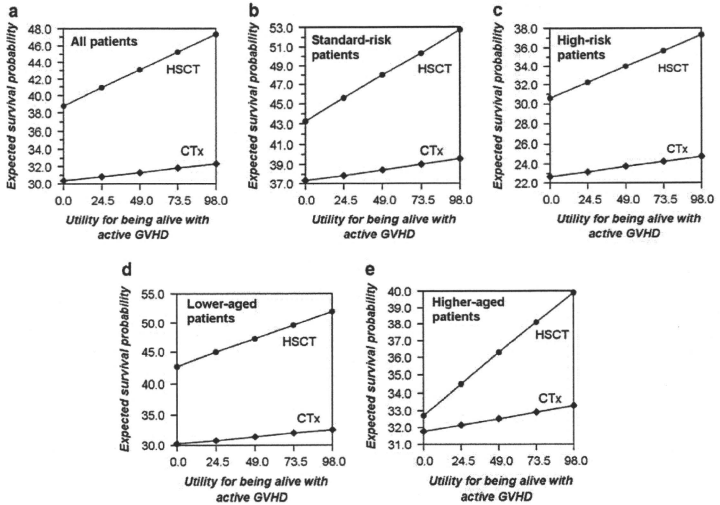

Figure 2 One-way sensitivity analysis for the utility for being alive with active GVHD. We performed one-way sensitivity analyses for the utility for being alive with active GVHD in the model, with adjustment for QOL. The superiority of allogeneic HSCT compared with chemotherapy (CTx) was consistently observed even with a wide plausible range of the utility in the whole population (**a**) and all subgroups (**b–e**).

Subgroup analyses

In subgroup analyses, both with and without adjustment for QOL, a better expected survival probability for HSCT was consistently observed in all subgroups (Table 4).

We also performed one-way sensitivity analyses in all subgroups. In the decision model without adjusting for QOL, varying each TP value in its plausible range did not affect the results of baseline analyses in all subgroups, except for higher-aged patients. In higher-aged patients, the result of the baseline analysis reversed only if the probability of LFS at 10 years following chemotherapy in first remission was more than 0.334. Even in the decision model with adjustment for QOL, varying each TP value did not affect the result of the baseline analyses in all subgroups, except for higher-aged patients. In higher-aged patients, the result reversed in favor of chemotherapy if the probability of LFS at 10 years without relapse following chemotherapy was more than 0.307 (Figure 3a) or the probability of overall survival at 10 years following HSCT in first remission was less than 0.413 (Figure 3b). On the other hand, non-relapse mortality at 10 years following chemotherapy did not affect the result. We also performed one-way sensitivity analyses for the utility of being alive with active GVHD ranging between 0 and 98. A higher expected survival probability for HSCT was retained in all subgroups (Figures 2b–e).

Discussion

Decision analysis is a statistical technique that aids the clinical decision-making process under uncertainty. This approach has also been used in situations in which a well-designed clinical trial is practically difficult to perform. In the present case, a prospective trial to randomly assign patients with ALL in first remission who have an HLA-matched sibling to undergo allogeneic HSCT or chemotherapy alone is practically difficult. Therefore, we tried to determine the optimal strategy in this clinical situation by using a decision analysis. We chose the 10-year survival probability as the primary outcome measure rather than life expectancy, as the cure rate, rather than how long they can survive, is important for young patients with acute leukemia to make a decision whether they should undergo allogeneic HSCT in first remission. When we performed the decision analysis using the 5-year survival probability as the primary outcome measure, however, the findings in this study did not change, as the survival curve nearly reaches a plateau after 5 years. Further, we adjusted for QOL by considering the presence or absence of persisting symptoms associated with chronic GVHD rather than by calculating quality-adjusted life years, as most patients who choose allogeneic HSCT may tolerate transiently impaired QOL and attach much importance to long-term QOL. Under these conditions, we decided to use a simple decision analysis model rather than a Markov model that allows probabilities and utilities to change with time, as the benefit of using a Markov model is limited in this situation. In addition, a large number of patients are required for the Markov model to define appropriate TPs that change with time. In this study, the number of patients was limited because we used data from the JALSG prospective studies to avoid biases of using retrospective data. We used the database of the JSHCT to calculate TPs in patients who underwent HSCT, because the number of patients who underwent HSCT was further limited in the JALSG prospective studies. However, outcomes after allogeneic HSCT in first remission were not significantly

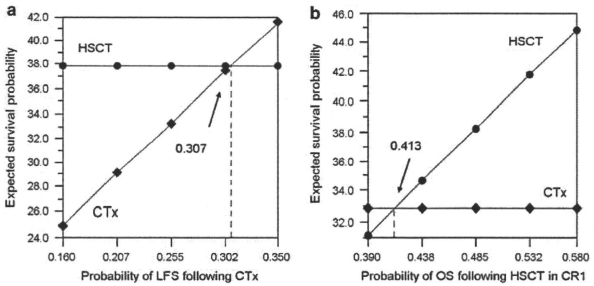

Figure 3 One-way sensitivity analysis in higher-aged patients. We performed one-way sensitivity analyses for all TPs in the decision model both with and without adjustment for QOL. In higher-aged patients, the result reversed if the probability of LFS at 10 years without relapse following chemotherapy (CTx) was more than 0.307 (**a**), or the probability of overall survival at 10 years following allogeneic HSCT in first complete remission (CR1) was less than 0.413 (**b**).

different among the JALSG prospective studies and the JSHCT database (data not shown).

In our baseline analysis both with and without adjustment for QOL, the superiority of HSCT in first remission was demonstrated in the whole population and also in all subgroups. In the whole population, probabilistic sensitivity analysis using a Monte Carlo simulation also supported this result. However, in one-way sensitivity analyses, we should note that the decision model was sensitive to the probability of LFS following chemotherapy in first remission in higher-aged patients (Figure 3a). The adaptation of intensified chemotherapy according to pediatric regimens has led to improved outcomes in adolescents and young adults,[20] and even in older patients in recent trials,[21] and therefore this decision might change in the future.

The risk stratification we used in subgroup analyses was different from that used in the MRC/ECOG study.[8] Therefore, we added subgroup analyses according to the risk stratification used in the MRC/ECOG study. In analyses without QOL adjustments, allogeneic HSCT in first remission was superior both in standard-risk (56.6 vs 36.2%) and high-risk (42.4 vs 33.3%) patients. With QOL adjustments, the similar tendency was observed in both standard-risk (52.6 vs 35.1%) and high-risk (39.4 vs 32.6%) patients. These findings were consistent with those based on our original risk stratification. In addition, we further subdivided patients into four different age categories: 15–25, 26–35, 36–45 and 46–54 years. The superiority of the decision to perform allogeneic HSCT in first remission was conserved in all age categories (data not shown).

A possible concern in this study was the long median duration of 152 days from achieving complete remission to allogeneic HSCT. In the current decision model, this long duration precluded allogeneic HSCT in first remission in about 20% of patients in the allogeneic HSCT branch (mainly because of early relapse), and thereby impaired the expected probability of survival for the decision to undergo allogeneic HSCT. In reality, a meta-regression analysis by Yanada *et al.*[3] revealed that compliance with allogeneic HSCT was significantly and positively correlated with survival.[3] Another fact to be noted is the low incidence of severe GVHD in Japanese patients, which might have favorably affected the decision to perform HSCT.[22] Therefore, the current conclusion should be cautiously applied to Western patients.

The QOL after HSCT is most strongly affected by the status of chronic GVHD, but it is difficult to determine the appropriate utility for each status of GVHD. Therefore, we performed a one-way sensitivity analysis with a wide plausible range of the utility for being alive with active GVHD. In our decision model, the superiority of HSCT was consistently observed regardless of the utility for being alive with active GVHD both in the whole population and in all subgroups (Figure 2).

In conclusion, to improve the long-term probability of survival, allogeneic HSCT in first remission is recommended for all adult patients with Ph-negative ALL who have an HLA-matched sibling. Even when we considered QOL, the superiority of HSCT was confirmed in the whole population and in all subgroups. However, this result might change by the adaptation of intensified chemotherapy, especially in higher-aged patients.

Conflict of interest

The authors declare no conflict of interest.

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Association between serum high-molecular-weight adiponectin level and the severity of chronic graft-versus-host disease in allogeneic stem cell transplantation recipients

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Association between serum high-molecular-weight adiponectin level and the severity of chronic graft-versus-host disease in allogeneic stem cell transplantation recipients

(Running title)

Association between adiponectin and chronic GVHD

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Abstract

Recently, a growing body of evidence has suggested that adiponectin, which is secreted by adipose tissues, plays a critical role in obesity-related and autoimmune diseases. We compared the concentrations of adiponectin among 26 normal subjects and 34 allogeneic stem cell transplantation recipients. The concentrations of adiponectin were significantly higher in recipients with cGVHD than those in subjects without cGVHD (21.7±11.0 vs 9.1±6.1 μg/ml in females ($P<0.001$), and 10.1±6.8 vs 4.3±2.9 μg/ml in males ($P=0.003$)). Multivariate analysis revealed that a higher concentration of adiponectin was associated with female gender (β-coefficient 8.2, $P<0.0001$) and the severity of cGVHD (β-coefficient 6.6, 12.7, and 15.6, $P <0.01$, each for mild, moderate, and severe cGVHD, respectively). In addition, adiponectin levels increased as cGVHD progressed, decreased as cGVHD improved, and did not change with stable cGVHD. In conclusion, adiponectin was associated with the severity of cGVHD, and might play a role in the pathophysiology of cGVHD.

Introduction

Chronic graft-versus-host disease (cGVHD) is a major problem following allogeneic stem cell transplantation (allo-SCT), and dramatically impairs the recipient's quality of life [1,2]. Clinical symptoms of cGVHD resemble those of autoimmune diseases, including scleroderma and sicca syndrome. Therefore, an immune abnormality similar to that in autoimmune diseases may play a role in the development of cGVHD, although the actual pathophysiology remains unknown [3]. In cGVHD, inflammatory cytokines that modulate T and B cells, such as tumor necrosis factor alpha (TNF-α) and soluble B-cell activation factor, have been well investigated [4,5]. However, it remains to be elucidated whether other endocrine substances may play a role in cGVHD. Recently, it has been revealed that adiponectin, an adipokine that is secreted by adipose tissues, is associated with immunity and inflammation, and may play a critical role in both obesity-related and autoimmune diseases [6-11]. Therefore, we compared the serum adiponectin levels among allo-SCT recipients and normal subjects to assess the association between adiponectin and cGVHD.

Patients and methods

We retrospectively reviewed the clinical records of 34 patients (21 with myeloid, 11 with lymphoid malignancies, and 2 with aplastic anemia) who received allo-SCT between March 2008 and March 2010 and who survived for at least 180 days after SCT. The diagnosis and the severity of cGVHD were determined based on the NIH classification [12]. In addition, we collected data regarding age, gender, and BMI of these patients as well as those of 26 normal healthy subjects as a control.

We measured the serum concentrations of high-molecular-weight (HMW) adiponectin by an enzyme-linked immunosorbent assay according to the manufacturer's instructions (Fujirebio Inc., Tokyo, Japan). To compare HMW-adiponectin levels among groups, we used the first samples obtained at least 6 months after SCT, and performed Student's t-test / ANOVA for categorical variables, and a regression analysis for continuous variables. Thereafter, multiple regression analysis was performed with backward stepwise selection. Furthermore, we calculated the ratios of later-to-prior HMW-adiponectin between each pair of consecutive samples in the same patients, and assessed the impact of the clinical changes in cGVHD on HMW-adiponectin concentrations using ANOVA after logarithmic conversion among recipients grouped according to worsening, stable, and improving cGVHD. Statistical significance was defined as a two-sided P-value of <0.05. This study was approved by the institutional review board of Jichi Medical University and all patients gave written informed consents for the cryopreservation and analyses of blood samples in accordance with the Declaration of Helsinki.

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