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演者（研究者にアンダーライン）	演題名	学会・シンポジウム名等	発表年
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飯田美奈子、**福田隆浩**、**池亀和博**、吉原 哲、小川啓恭、**谷口修一**、**高見昭良**、安部康信、日野雅之、衛藤徹也、熱田由子、田中淳司、**鈴木律朗**	我が国における血縁同種造血幹細胞移植での Mycophenolate Mofetil (MMF) 使用全国実態調査結果報告	第 71 回日本血液学会学術集会（京都）	2009

演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会･ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
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演者（研究者にｱﾝﾀﾞｰﾗｲﾝ）	演　題　名	学会・ｼﾝﾎﾟｼﾞｳﾑ名等	発表年
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Kim SW, Yoon SS, **Suzuki R**, Yi HG, Ago H, Imamura M, Wake A, Yoshida T, Lee JJ, Kim JS, Maeda Y, Izutsu K, Kang HJ, Lee JH, Kim HC, Suzumiya J, Matsuno Y, Kim CW, Nagafuji K, Takaue Y, Harada M, Kim CS.	Autologous Versus Allogeneic Hematopoietic Stem Cell Transplantation (SCT) for Peripheral T-cell Lymphomas (PTCLs): Japan and Korea Cooperative Study with 330 Patients.	Blood (ASH Annual Meeting Abstracts) 114: 901	2009
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Ⅴ．研究成果の刊行物（論文別刷）

A Markov decision analysis of allogeneic hematopoietic cell transplantation versus chemotherapy in patients with acute myeloid leukemia in first remission

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Various prospective trials have been performed to assess the roles of allogeneic hematopoietic cell transplantation (allo-HCT) and chemotherapy in patients with acute myeloid leukemia (AML) in first complete remission (CR1). However, the results have not always been consistent, and there has been a limited evaluation of quality of life (QOL) in these postremission strategies. We performed a Markov decision analysis that enabled us to compare survival outcomes with a QOL evaluation using a database of 2029 adult AML patients who achieved CR1. The Markov decision model compared 2 strategies: allo-HCT or chemotherapy in CR1. Patients who had intermediate- or unfavorable-risk AML had a longer life expectancy when they received allo-HCT in CR1 than patients treated with chemotherapy alone. Likewise, patients who had a suitable related donor who received allo-HCT in CR1 had a longer life expectancy. The life expectancy was shortened to a greater degree by adjustment for QOL in the allo-HCT group. Nevertheless, QOL-adjusted life expectancies in most of the subgroups remained longer in the allo-HCT group than in the chemotherapy group. Our results showed that older patients with a related donor and younger patients with unfavorable cytogenetics benefited the most from allo-HCT in CR1. (*Blood.* 2011;117(7):2113-2120)

Introduction

Although 60%-80% of patients with acute myeloid leukemia (AML) achieve first hematologic complete remission (CR1) with chemotherapy, a substantial number of patients have an individualized risk of relapse.[1] Allogeneic hematopoietic cell transplantation (allo-HCT) has been established as a powerful treatment method to reduce the risk of relapse in patients with AML. However, this approach still leaves concerns associated with a certain probability of nonrelapse mortality. Although several prospective trials that used genetic allocation have been performed to clarify the roles of postremission strategies, the results have not always been consistent.[2-9] The role of allo-HCT in patients with AML in certain subgroups, including patients with intermediate-risk AML and elderly patients who have remained in CR1, remains unclear. A large meta-analysis that considered many of these prospective studies reported that allo-HCT in CR1 provided survival advantages not only in an unfavorable-risk group but also in an intermediate-risk group.[10] Even with these numerous studies performed in a prospective setting, it is still controversial to simply define allo-HCT as a better decision because of concerns about various late effects such as graft-versus-host disease (GVHD) that might lower the quality of life (QOL) after cure of the disease.

A decision analysis is a statistical technique that is used to help decision making under uncertain conditions with the assumption of a QOL evaluation.[11] When it is combined with a Markov process, it gives a flexible analytical method that makes it possible to track clinical events that occur after a certain decision with different probabilities and desirability over time.[12] This technique can offer valuable information about what clinical decision should be taken by quantitatively integrating the risks and benefits of a certain decision, and, hence, has been widely applied in making decisions in various fields. For example, in the field of hematology, on the basis of the results of a Markov decision analysis, Lee et al[13] reported the indications of allo-HCT for chronic myeloid leukemia in the era before imatinib, and Cutler et al[14] elucidated the recommended timing of allo-HCT for younger patients with myelodysplastic syndrome. Regarding AML, Sung et al[15] reported the results of a decision analysis with a conventional decision tree concerning consolidation strategies for patients in CR1. However, a Markov decision analysis has not yet been reported for postremission strategies in AML in CR1. To address this point, we performed a Markov decision analysis with the use of clinical information collected from 2029 patients.

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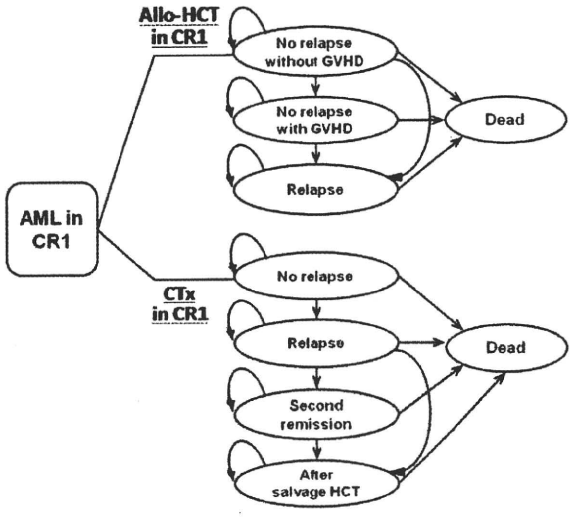

Figure 1. Markov decision model. Markov model that compares allo-HCT in CR1 and chemotherapy in CR1 is shown. Possible health states for each of the 2 groups are indicated in circles. Arrows indicate possible transitions between states. CR1 indicates first complete remission; allo-HCT, allogeneic hematopoietic cell transplantation; CTx, chemotherapy; and GVHD, graft-versus-host disease.

Methods

Data source

The study protocol was approved by the Institutional Review Board at National Cancer Center Hospital. We constructed a new database that included the clinical data of adult patients (age 16-70 years) whose conditions were diagnosed as AML by the World Health Organization classification between 1999 and 2006 and who had achieved CR1 after 1 or 2 courses of induction chemotherapy. Clinical information on > 2600 patients was collected from 70 institutions across the country. Patients with biphenotypic leukemia who were treated with chemotherapy for acute lymphocytic leukemia; patients who had extramedullar AML without marrow invasion, an extramedullary lesion that did not totally disappear after remission induction chemotherapy, or acute promyelocytic leukemia; and patients who received autologous HCT in CR1 were excluded from the analysis. Consequently, a total of 2029 patients were considered for this analysis.

Decision strategy

The primary decision examined in this study was whether to perform allo-HCT in patients with AML who remained in CR1. Statistical analyses were performed as of January 2010 with the use of the software package TreeAge Pro 2009 (TreeAge Software Inc) and the SPSS software package (SPSS Inc).

Markov model. We constructed a Markov decision model to compare 2 strategies: performing allo-HCT in CR1 (HCT group) and continuing chemotherapy without allo-HCT in CR1 (CTx group; Figure 1). The possible health states that were considered to occur after each decision/strategy included, for the HCT group, (1) no relapse without GVHD, (2) no relapse with GVHD, (3) relapse, and (4) dead, and for the CTx group, (1) no relapse, (2) relapse, (3) second remission, (4) after salvage allo-HCT, and (5) dead. The "GVHD" state included chronic extensive GVHD. The "dead" state included death from any cause. A schematic of the tree file is shown in supplemental Figure 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article.

State transition probabilities. Transition probabilities between the states were calculated from the information in the database collected for this analysis as described in "Data source." The probabilities of state transition were allowed to vary over time. As a result, patients were distributed in various health states with different proportions along with cycle advances, that is, as time advanced from CR1, as shown in Figure 2. To take into account patients who were unable to receive allo-HCT in CR1 even though they had made a decision to receive allo-HCT, patients who died or relapsed within 3 months from CR1 were excluded from the database when we calculated the probabilities. The cycle length between state transitions has previously been set at the time considered to represent the clinical features and decision-making process for the target disease. In a Markov decision analysis that targeted myelodysplastic syndrome,[14] the cycle length was set at 6 months. In this analysis that targets patients with AML, we chose a shorter cycle length (3 months), and the analysis was performed for 40 cycles (10 years). The results are presented as life expectancy (LE), which is the average duration of life when patients are followed up for 10 years.

QOL utilities. We also assessed QOL-adjusted life expectancy (QALE) for the HCT and CTx groups. The time spent in each health state was adjusted for the estimated QOL that patients experienced while they remained in that state, which was represented by a utility value. In this study, utility values were derived from a questionnaire (supplemental Figure 2) that used a visual analog scale and was presented to 35 physicians who were familiar with the treatment of AML. Among them, 25 were physicians who were mainly involved in transplantation, and 10 were physicians mostly involved in chemotherapy with knowledge of transplantation. The utility values were expressed as numerical values between 0 (a

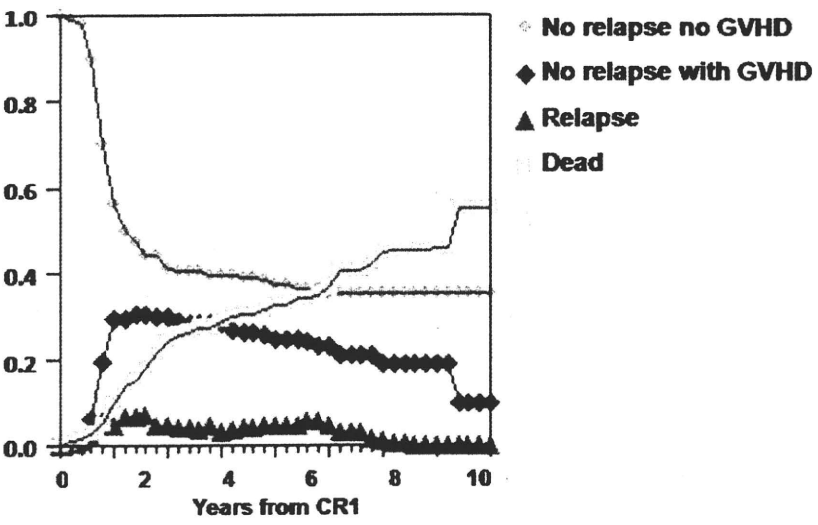

Figure 2. Distribution of patients in each health state. Distribution of patients with intermediate-risk AML in each health state is shown. Transition probabilities between the states were calculated for each subgroup with the use of the database. The probabilities of state transition were allowed to vary along with the cycle (1 cycle = 3 months) advances, depending on the states that the cohorts move from and to. As a result, the patients were distributed in each health state in changing proportions at different times from CR1. GVHD indicates graft-versus-host disease; and CR1, first complete remission.

Table 1. Quality-of-life utilities

	Median	Range
Allo-HCT in CR1		
No relapse without GVHD	0.90	0.60-1.00
No relapse with GVHD	0.60	0.40-0.80
Relapse	0.30	0.20-0.70
Chemotherapy in CR1		
No relapse	0.90	0.80-1.00
Relapse	0.50	0.20-0.80
Second remission	0.80	0.40-0.95
After salvage allo-HCT	0.66	0.10-1.00

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR1, first complete remission; and GVHD, graft-versus-host disease.

health state equivalent to dead) and 1 (perfect health) (Table 1) and were used to adjust for QOL by being multiplied by the expected length of life for each state in each cycle. For long-term survivors who developed chronic extensive GVHD, the utility value was changed on the basis of the previously reported probability of the discontinuation of immunosuppressive treatment.[16,17]

Comparison of HCT with CTx in CR1 and sensitivity analyses. Both LE and QALE were analyzed for the HCT group and the CTx group. LE and QALE, which represent the average expected duration of life in 10-year follow-up from CR1, were obtained from the area under the survival curves depicted by TreeAge Pro software. An annual discount rate of 3% was used for all analyses. Subgroup analyses were performed on the basis of patient age, the Southwest Oncology Group (SWOG) cytogenetic classification,[2] and donor availability. We performed sensitivity analyses to test the robustness of our conclusions. Variable measures that were tested in the sensitivity analysis included the range of patients who were excluded from the database on the assumption that they were unable to receive the decided treatment, the plausible range of QOL utilities, 95% confidence intervals of the state transition probabilities, and the age range of subgroups.

Results

Patients

A total of 2029 patients were eligible for this analysis (Table 2). The median age was 50 years, and the median follow-up of the surviving patients was 49.8 months (range, 0.2-116.3 months). The proportions of patients with favorable, intermediate, unfavorable, and unknown cytogenetic risk according to the SWOG criteria were 19%, 52%, 18%, and 11%, respectively. Therapies performed at CR1 were allo-HCT in 494 patients (24%) and chemotherapy in 1535 patients (76%). The HCT group included all the 494 patients who received allo-HCT in CR1. The median interval from CR1 to allo-HCT was 4.7 months (range, 0-37 months). Among patients who were treated with chemotherapy in CR1, 118 patients who died or relapsed within 3 months were excluded when calculating state transition probabilities on the assumption that they might have decided to receive allo-HCT while they remained in CR1. As a consequence, 1417 patients, including 478 who received allo-HCT after their first relapse, were included in the CTx group (Figure 3). The patients in the HCT group were younger and were more often associated with unfavorable features compared with those in the CTx group. Table 3 and Figure 3 show donor availability and actual application of allo-HCT in CR1. Among 1076 patients for whom human leukocyte antigen (HLA) was typed in CR1, 431 had HLA-matched or 1-antigen (Ag)–mismatched related donors (40%). Donor group included the 431 patients who had a suitable related donor. Among them, 243 actually received allo-HCT in CR1 (related donor, 240; unrelated donor, 3). The no-donor group included the 645 patients who did not find a related donor and 953 for whom HLA was not typed in CR1. Among them, 251 received allo-HCT in CR1 from an alternative donor (unrelated bone marrow, 177; unrelated cord blood, 62; haploidentical related donor, 12). In both the donor and no-donor groups, subgroup analyses were separately performed by comparing patients who received allo-HCT in CR1 (HCT group) and patients who did not (CTx group). Overall survival curves obtained by a Kaplan-Meier estimation of all of the patients registered in our original database stratified according to the SWOG classification and the treatment chosen in CR1 are shown in supplemental Figure 3. Survival curves depicted by TreeAge Pro are shown in supplemental Figure 4.

Markov decision analysis

The discounted LE and QALE for the HCT and CTx groups were analyzed for patients of all ages, younger patients (16-49 years) and older patients (50-70 years; Table 4). In each age group, LE and QALE were analyzed in different cytogenetic subgroups and donor-availability subgroups.

Analysis of all patients. An analysis that included patients of all ages showed that LE in the HCT group was 3 months longer than that in the CTx group (69.7 vs 66.7 months; Table 4). After we adjusted for QOL, QALE in the HCT group was only 0.5 months longer than that in the CTx group (55.9 vs 55.4 months). The LE was generally shortened to a greater degree in the HCT group after adjustment for QOL. This trend was consistent throughout all of the subgroups.

We performed subset analyses according to cytogenetic risk stratified according to the SWOG criteria. Patients with favorable-risk AML in the CTx group had a longer LE than patients in the HCT group. In contrast, patients with intermediate, unfavorable, and unknown-risk AML in the HCT group had a longer LE than patients in the CTx group (intermediate, 73.6 vs 66.4 months; unfavorable, 61.6 vs 53.4 months). Although QALE was shortened to a greater degree in the HCT group, we found that QALE

Table 2. Patient characteristics

Characteristics	Allo-HCT in CR1	CTx in CR1	All patients	P*
No. of patients	494	1535	2029	
Median age, y	42	53	50 (16-70)	< .001
Cytogenetic risks (SWOG)				< .001
Favorable, n (%)	29 (6)	360 (23)	389 (19)	
Intermediate, n (%)	272 (55)	777 (51)	1049 (52)	
Unfavorable, n (%)	115 (23)	246 (16)	361 (18)	
Unknown, n (%)	78 (16)	152 (10)	230 (11)	
FAB				< .001
M1, 2, 4, 5, n (%)	339 (81)	1345 (93)	1684 (90)	
M0, 6, 7, n (%)	81 (19)	104 (7)	185 (10)	
WBC count				.123
≤ 20 000 μ/L, n (%)	303 (65)	887 (61)	1190 (62)	
> 20 000 μ/L, n (%)	163 (35)	570 (39)	733 (38)	
Remission induction courses				< .001
1 course, n (%)	340 (69)	1276 (83)	1616 (80)	
2 courses, n (%)	154 (31)	259 (17)	413 (20)	
Dysplasia				< .001
No, n (%)	337 (68)	1264 (83)	1601 (79)	
Yes, n (%)	156 (32)	268 (17)	424 (21)	

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CTx, chemotherapy; SWOG, Southwest Oncology Group; FAB, French-American-British; and WBC, white blood cell.

*Comparing "Allo-HCT in CR1" with "CTx in CR1."

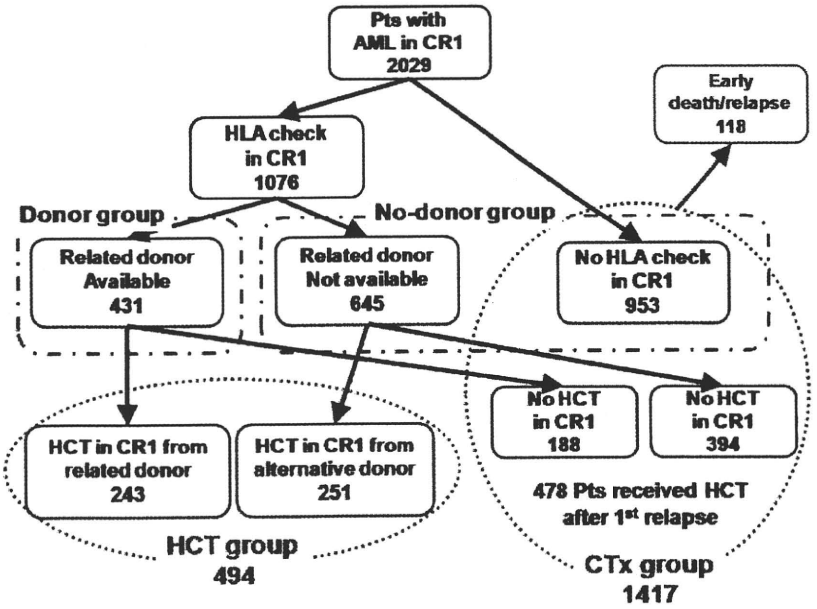

Figure 3. Patient flow. The flow of HLA check, donor availability, and actual application of allo-HCT in CR1 are shown. Among the total of 2029 patients with AML in CR1, 494 received allo-HCT in CR1 and were included in the HCT group. Among the remaining 1535 patients, 118 patients who died or relapsed within 3 months were excluded to take into account patients who were unable to receive allo-HCT in CR1 even though they had made a decision to receive HCT in CR1. Consequently, 1417 patients were included in the CTx group. Among them, 478 received allo-HCT after first relapse. The donor group included the 431 patients who had a suitable related donor. The no-donor group included the 645 patients who did not find a related donor and 953 for whom HLA was not typed in CR1. CR1 indicates first complete remission; and HCT, hematopoietic cell transplantation.

remained longer in the HCT group for all cytogenetic risks except for the favorable-risk group (favorable, 56.0 vs 64.3 months; intermediate, 59.4 vs 55.6 months; unfavorable, 47.6 vs 44.4 months). In the analysis of AML other than favorable risk, patients in the HCT group had a longer LE and a longer QALE than patients in the CTx group (LE, 69.5 vs 62.5 months; QALE, 55.8 vs 52.0 months).

We also performed subset analyses on the basis of the availability of a related donor. Patients who were known to have an HLA-matched or 1-Ag– mismatched related donor (donor group) in the HCT group had a longer LE and a longer QALE than patients in the CTx group (LE, 72.2 vs 63.0 months; QALE, 57.6 vs 49.9 months). However, in patients who did not have a suitable related donor (no-donor group), there were no differences in LE or QALE between the HCT and CTx groups (LE, 67.7 vs 67.0 months; QALE, 54.6 vs 54.4 months). Analyses of the donor and no-donor groups were also conducted with the database whereby the favorable-risk patients were excluded. There was almost no change in LE and QALE in the HCT group (less than a month) compared with the results obtained with the whole database. However, LE and QALE in the CTx group were shortened by several months by excluding the patients with favorable-risk AML from analysis. Consequently, in the donor group, the differences of LE and QALE between the HCT and CTx group increased (LE, 72.0 vs 60.5 months; QALE, 57.2 vs 47.6 months). Meanwhile in the no-donor group, LE and QALE in the HCT group became longer than those in the CTx group (LE, 67.3 vs 64.2 months; QALE, 54.5 vs 52.2 months). Survival curves that compare the HCT and CTx groups in these subgroups depicted by TreeAge Pro software are shown in Figure 4.

Analysis of younger patients. For younger patients, LE and QALE were analyzed with the data from patients aged 16-49 years

Table 3. Donor availability and transplantation in CR1

Characteristics	No HLA check in CR1	HLA check in CR1 (n = 1076)			
		Related donor available/HCT+	Related donor available/HCT–	Related donor not available/HCT+	Related donor not available/HCT–
Total no. of patients	953	243	188	251	394
Cytogenetic risks (SWOG)					
Favorable, n (%)	233 (24)	12 (5)	47 (25)	17 (7)	80 (20)
Intermediate, n (%)	496 (52)	140 (58)	84 (45)	132 (53)	197 (50)
Unfavorable, n (%)	139 (15)	52 (21)	38 (20)	63 (25)	69 (18)
Unknown, n (%)	85 (9)	39 (16)	19 (10)	39 (16)	48 (12)
No. of younger patients, n (%)	257	167	127	175	267
Cytogenetic risks					
Favorable, n (%)	106 (41)	8 (5)	35 (28)	16 (9)	60 (22)
Intermediate, n (%)	101 (39)	97 (58)	55 (43)	82 (47)	125 (47)
Unfavorable, n (%)	30 (12)	39 (23)	27 (21)	49 (28)	50 (19)
Unknown, n (%)	20 (8)	23 (14)	10 (8)	28 (16)	32 (12)
No. of older patients, n (%)	696	76	61	76	127
Cytogenetic risks					
Favorable, n (%)	127 (18)	4 (5)	12 (20)	1 (1)	20 (16)
Intermediate, n (%)	395 (57)	43 (57)	29 (48)	50 (66)	72 (57)
Unfavorable, n (%)	109 (16)	13 (17)	11 (18)	14 (18)	19 (15)
Unknown, n (%)	65 (9)	16 (21)	9 (15)	11 (14)	16 (13)

CR1 indicates first complete remission; HLA, human leukocyte antigen; HCT, allogeneic hematopoietic cell transplantation; and SWOG, Southwest Oncology Group.

Table 4. Discounted life expectancy

	All patients				Younger patients (median age, 35 y)				Older patients (median age, 60 y)			
	LE		QALE		LE		QALE		LE		QALE	
Decision at CR1	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx	Allo-HCT	CTx
Total	69.7	66.7	55.9	55.4	71.4	73.2	57.7	60.2	65.8	60.0	52.1	50.6
Cytogenetic risks (SWOG)												
Favorable	69.6	77.0	56.0	64.3	67.0	82.3	53.8	67.6				
Intermediate	73.6	66.4	59.4	55.6	76.2	75.1	62.0	62.4	68.5	60.7	54.5	51.4
Unfavorable	61.6	53.4	47.6	44.4	62.8	55.3	48.7	44.8	61.6	53.3	46.0	45.0
Unknown	65.6	59.3	54.1	46.8	67.4	68.3	56.3	53.6	63.1	48.8	50.6	38.9
Other than favorable	69.5	62.5	55.8	52.0								
Donor availability												
Related donor	72.2	63.0	57.6	49.9	73.0	67.6	58.3	54.2	73.4	53.2	57.7	40.4
No related donor	67.7	67.0	54.6	54.4	71.0	70.7	57.7	57.2	57.4	57.7	45.4	46.8
Donor availability (other than favorable-risk)												
Related donor	72.0	60.5	57.2	47.6								
No related donor	67.3	64.2	54.5	52.2								

Life expectancies are shown in months.
LE indicates life expectancy; QALE, quality of life–adjusted life expectancy; allo-HCT, allogeneic hematopoietic cell transplantation; and CTx, chemotherapy.

(median 35 years). In the HCT group, LE in younger patients was 6 months longer than that in older patients (71.4 vs 65.8 months). In the CTx group, LE in younger patients was longer than that in older patients by more than a year (73.2 vs 60.0 months).

Younger patients with favorable-risk AML had both a longer LE and a longer QALE in the CTx group than in the HCT group. Allo-HCT in CR1 among younger patients was associated with a longer LE in both the unfavorable-risk group (62.8 vs 55.3 months) and donor group (73.0 vs 67.6 months). After we adjusted for QOL, these patients in the HCT group had a longer QALE than those in the CTx group (unfavorable, 48.7 vs 44.8 months; donor group, 58.3 vs 54.2 months). Younger patients with intermediate-risk AML in the HCT group had a slightly longer LE than those in the CTx group (76.2 vs 75.1 months). However, QALE did not improve when they received allo-HCT in CR1 (62.0 vs 62.4 months).

Analysis of older patients. The outcomes for older patients were analyzed with the data from patients aged 50-70 years (median, 60 years). Older patients who received allo-HCT in CR1 had a longer LE than patients who received chemotherapy in all subgroups, except for the no-donor group (intermediate, 68.5 vs 60.7 months; unfavorable, 61.6 vs 53.3 months; donor group, 73.4 vs 53.2 months). The data available for favorable-risk patients who received allo-HCT in CR1 were insufficient to perform an

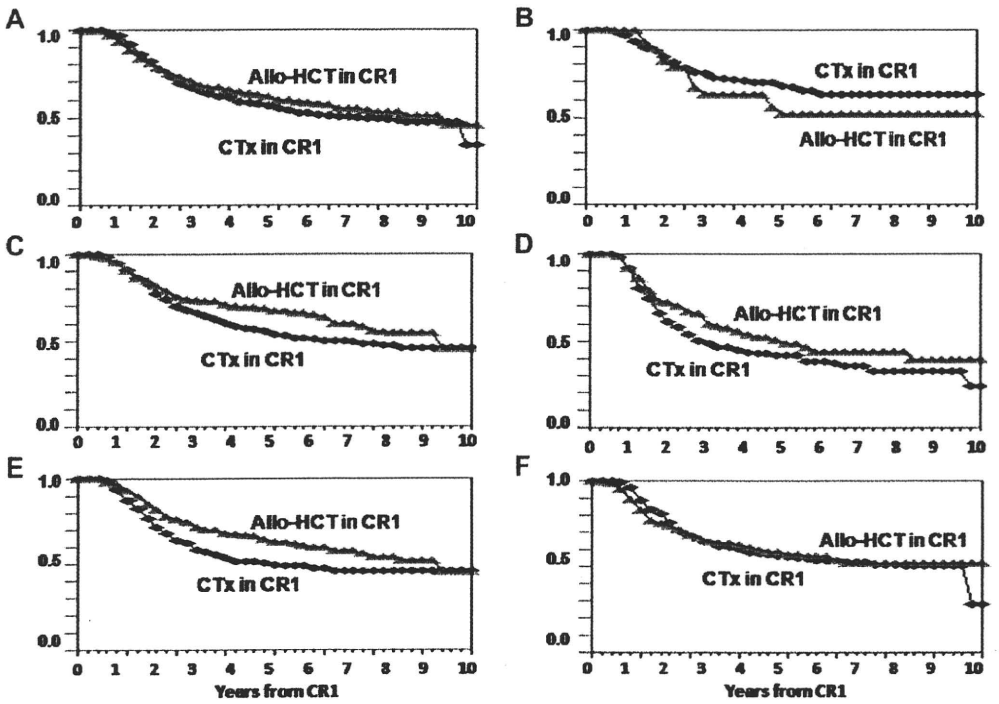

Figure 4. Survival curves of allo-HCT versus CTx by TreeAge. The overall survival curves of the HCT and CTx groups depicted by TreeAge Pro 2009 in (A) total patients, (B) SWOG favorable-risk group, (C) intermediate-risk group, (D) unfavorable-risk group, (E) donor group, and (F) no-donor group. allo-HCT indicates allogeneic hematopoietic cell transplantation; CTx, chemotherapy; and CR1, first complete remission.

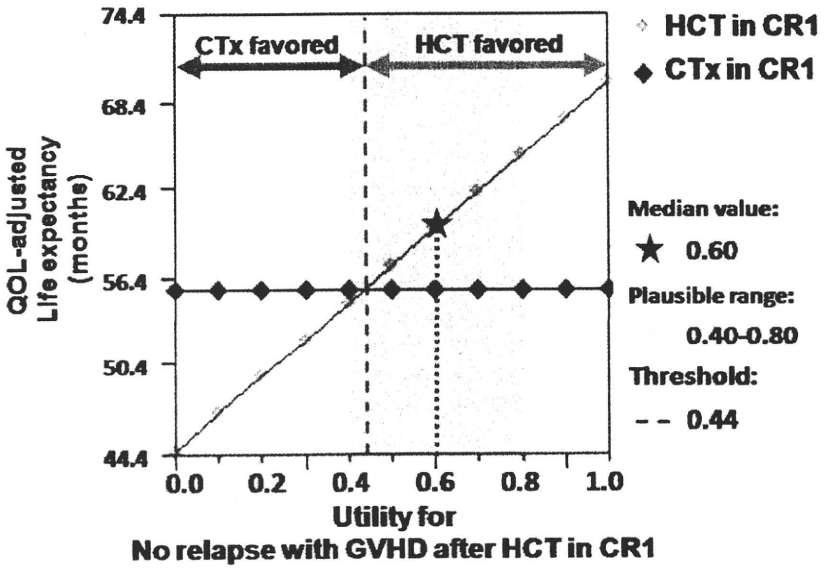

Figure 5. One-way sensitivity analysis. One-way sensitivity analysis for the utility of the state "No relapse with GVHD" after allogeneic transplantation in CR1 among patients with intermediate-risk AML is shown. The green dot represents the QOL-adjusted life expectancy when allo-HCT was performed in CR1. The blue dot represents the QOL-adjusted life expectancy when treated with chemotherapy in CR1. The median value of the utility for this state provided by physicians was 0.60, shown as a red star. At the median value, QOL-adjusted life expectancy in the HCT group is shown to outweigh that in the CTx group. The threshold value at which the favored decision is altered was 0.44, shown as a black dotted line. The plausible range of the utility provided by physicians was 0.40-0.80, shown as a red transparent square. Because the threshold value, 0.44, was included within the plausible range, this sensitivity analysis indicates that this result favoring HCT may be altered, depending on how the QOL of chronic GVHD is evaluated. Such results that favored a decision may change within the plausible range are interpreted as "sensitive." If the plausible range was provided in 0.50-0.80, this result would turn to "not sensitive," indicating that the favored decision does not change. QOL indicates quality of life; CR1, first complete remission; HCT, allogeneic hematopoietic cell transplantation; CTx, chemotherapy; and GVHD, graft-versus-host disease.

analysis. Because of the large decrease in LE in the CTx group among older patients, differences in LE between the HCT and CTx groups became more prominent in older patients than in younger patients. Although the difference in the duration of life between the HCT and CTx groups decreased after we adjusted for QOL, we found that older patients in the HCT group had a longer QALE in the intermediate- and unfavorable-risk groups. The difference in QALE between the HCT and CTx groups was most prominent among older patients who had a suitable related donor (donor group, 57.7 vs 40.4 months).

Sensitivity analysis and external validation. Sensitivity analyses were performed for the assumption of "patients who were unable to receive allo-HCT in CR1 despite the decision to perform allo-HCT," the plausible range of QOL utilities (Figures 5-6; supplemental Figure 5), 95% confidence intervals of the state transition probabilities, and the age range. We found that the optimal decisions could be altered in both directions, allo-HCT favored versus CTx favored, by changing the population that was excluded from the database, changing the utility values within the plausible range of physicians' opinions, changing the state transition probabilities within the range of the confidence interval, and changing the cutoff point for the age at which the age subgroups were divided. We also compared the overall survival curves depicted by TreeAge Pro software with the use of our database with those obtained by a Kaplan-Meier estimation as reported in prospective studies from other countries.[2,6] The curves had similar shapes (supplemental Figure 4).

Discussion

We performed a decision analysis that applied a Markov process to evaluate 2 postremission strategies: allo-HCT and CTx in AML in

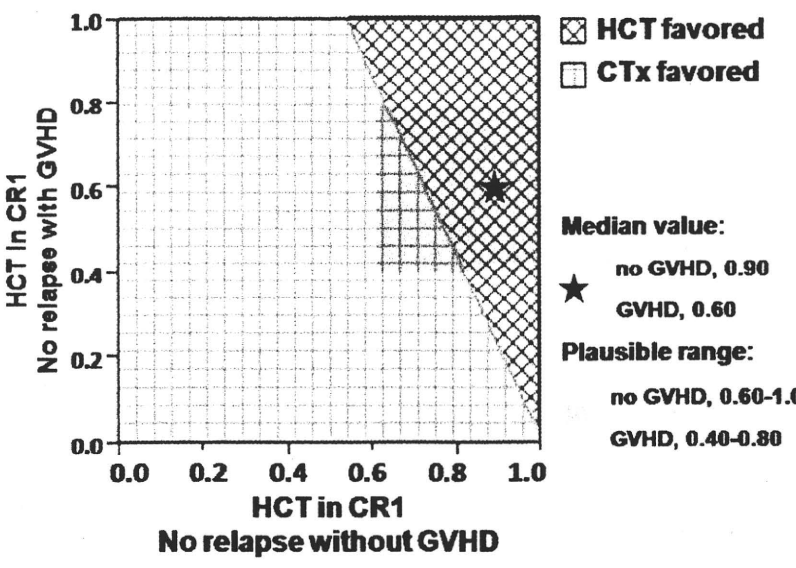

Figure 6. Two-way sensitivity analysis. Two-way sensitivity analysis for the utilities of the states "No relapse without GVHD" and "No relapse with GVHD." The blue area represents the range in which HCT is favored. The green area represents the range in which CTx is favored. Although the median value (0.90 for "without GVHD" and 0.60 for "with GVHD," shown as a red star) indicates that HCT in CR1 is favored, the plausible range (0.60-1.00 for "without GVHD" and 0.40-0.80 for "with GVHD," shown as a red transparent square) overlaps the threshold line. This result is interpreted as "sensitive," which means the outcome is changeable within the plausible range of QOL evaluation provided by physicians. CR1 indicates first complete remission; HCT, allogeneic hematopoietic stem cell transplantation; CTx, chemotherapy; and GVHD, graft-versus-host disease.

CR1. Our results showed that the LE of patients with intermediate- and unfavorable-risk AML were longer when they received allo-HCT in CR1. We also found that patients who were known to have a suitable related donor had a longer LE in the HCT group. After adjustment for QOL, QALE in most of these subgroups remained longer in patients who received allo-HCT in CR1 than in patients who received chemotherapy.

In subset analyses according to the cytogenetic risk, we showed that favorable-risk patients had a longer LE and a longer QALE in the CTx group, which is consistent with previous reports. However, the results in favorable-risk patients may not be reliable because only a few patients with favorable-risk AML received allo-HCT in CR1 and patients in the HCT group may have had specific reasons (eg, 2 courses of remission induction chemotherapy or antecedent hematologic dysplasia).

In intermediate-risk and unfavorable-risk patients, LE was longer in the HCT group. This result was consistent with that of a large meta-analysis.[10] If we integrate the assumption about the QOL obtained after the 2 strategies using utility values provided by physicians, the LE was shortened to a greater degree in the HCT group. This observation may indicate that there are more concerns about the deterioration of the QOL after allo-HCT than after chemotherapy alone. However, we still found that the QALE was longer in the HCT group, except for younger intermediate-risk patients.

In subset analyses that were based on donor availability, we found that patients who had an HLA-matched or 1-Ag–mismatched related donor had a longer LE and a longer QALE when allo-HCT was performed during CR1. A purposeful delay of allo-HCT has not been fully studied in patients with AML when they have a suitable related donor.[6] This result may recommend that we consider allo-HCT in CR1 rather than wait until after relapse when a suitable related donor is available. LE in older patients who received allo-HCT from a suitable related donor was even comparable to that in younger patients (73.0 vs 73.4 months), which led to a more conspicuous superiority of allo-HCT compared with CTx when older patients had a suitable related donor. In addition, the QALE of older patients with a related donor was 17 months longer in the HCT group than in the CTx group. This result suggests that allo-HCT in CR1 from a suitable related donor for older patients may provide an improved outcome even after we take into account transplantation-related toxicities, which are generally a greater concern among older patients.[18] However, among patients who did not have a suitable related donor, we did not find any advantages of allo-HCT from an alternative donor in CR1 compared with the CTx group. In recent years, the outcomes of allo-HCT from a matched related donor and that from a matched unrelated donor have been reported to be comparable.[19] Because this database included the clinical information of patients treated between 1999 and 2006, most of the unrelated bone marrow (BM) donor sources were selected on the basis of HLA serum matches and not on allele matches. In addition, our database included 1-Ag–mismatched unrelated BM and unrelated cord blood as alternative donors. Regarding the indications for allo-HCT from an alternative donor, further studies may be needed to evaluate whether there is a population that benefits from allo-HCT from well-matched unrelated BM.

The ability to consider QOL is one of the advantages of performing a decision analysis. We adjusted for QOL by applying QOL utility values provided by physicians. Utility values for various health states were obtained over a wide range. This observation may indicate that, even for the same patient, different therapeutic strategies may be chosen at the discretion of the physician. Another reason why the range of utility was broad may be the diverse symptoms and QOL within the same health state, such as the severity of "extensive chronic GVHD."[20,21] Consequently, in our study, sensitivity analyses showed that a better decision with a higher QALE was frequently altered to the other decision within the plausible range of utility values provided by physicians. There were no significant difference between the values provided by transplantation physicians and chemotherapy physicians. However, interestingly, median values of QOL utility in our study were lower than those used in prior analyses performed in North America. For example, although the utility for "no relapse with GVHD" was set at 0.6 (range, 0.4-0.8) in our study, this value was set at around 0.9 in other studies.[13-15,22] This trend was more prominent in the HCT group, which might indicate differences in approaches to estimating the same complications that may be due to ethnicity or differences in the contents of questionnaires.

It might be ideal to evaluate QALE based on QOL utility values obtained from patients who actually live with various disease states.[23,24] However, most prior studies on decision analysis in this field have used utility values provided by physicians.[13-15] Sung et al[15] stated that their utility values provided by physicians were consistent with those provided by patients in the European Organization for Research and Treatment of Cancer and Gruppo Italiano Malattie Ematologiche dell' Adulto trial.[24] Patients may even give diverse QOL values for a certain health state according to differences in age, background, and philosophy. We believe that a QOL validation by patients is an important issue and is worth being pursued in another study.

Our data surely reflect the nature of a retrospectively collected database, including a diverse heterogeneity in treatment strategies chosen after the achievement of CR1. However, it may be difficult to obtain a database that was collected purely prospectively, especially in patients who were treated with chemotherapy alone. Therefore, we considered that this database, which consists of the clinical information for 2029 patients, was sufficient for us to perform this analysis. Another concern is that, because we collected clinical data on Japanese patients, the application of these results to other ethnic populations needs to be carefully evaluated. However, we have shown that the survival curves obtained from this analysis are similar to those reported in prospective studies from other countries. In decision analysis, the P value is not used to show the "significantly" better decision. Sensitivity analysis is a way to investigate the robustness of our conclusions when various parameters are changed within a possible range. It might be difficult to draw a definite conclusion in this study because, as a result of the sensitivity analysis, a favorable decision could be switched to the other decision. Nevertheless, we have been able to show that a decision analysis with a Markov model can be effectively used to evaluate the QOL-adjusted survival outcomes of allo-HCT versus chemotherapy in CR1.

In summary, by using a Markov decision analysis that was based on an original database collected for this study, we have shown that patients with intermediate- and unfavorable-risk AML and patients who had a suitable related donor had a longer LE and a longer QALE when they received allo-HCT in CR1. A subgroup analysis showed that older patients with a suitable related donor benefited the most from allo-HCT in CR1. Although it is clear that both methods of treatment still require improvement, we believe

that this observation serves as an important guide for considering the indications for allo-HCT in AML in CR1 by incorporating the evaluation of QOL. Adjustment for QOL with the use of utility values provided by patients who live with the disease should add valuable clues for weighing the value of a postremission strategy for each person. In addition, an investigation that applies a prospectively collected database for a multiethnic population should help to further show the roles of allo-HCT and chemotherapy in AML in CR1.

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Authorship

Contribution: S.K. designed the study, prepared the data file, performed the analysis, interpreted data, and wrote the manuscript; T. Yamaguchi was primarily responsible for the study design, data analysis, and interpretation of the data; S.M., N.U., H.K., K.U., T. Yamashita, M.W., K.Y., S.Y., Y. Nawa, J. Taguchi, J. Takeuchi, J. Tomiyama, and Y. Nakamura obtained the patients' data and interpreted data; I.M. reviewed the cytogenetic reports and interpreted data; Y.K. helped to design the study and to interpret data; Y.T. interpreted data and helped to write the paper; and T.F. was primarily responsible for the entire paper as an accurate and verifiable report.

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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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臨床研究

我が国における同種造血幹細胞移植患者の長期フォローアップの実態調査

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造血幹細胞移植数の増加と移植技術の進歩とともに晩期合併症のマネジメントの必要性も増している。我が国における造血幹細胞移植患者の長期フォローアップについて全国の移植施設に対して質問紙を用いた郵送による調査を施行した。194 施設中 100 施設から回答を得た。移植後患者一人当たり診療時間中央値 12.5 分，移植患者に特化した外来枠を設けている施設 5%。慢性 GVHD について NIH consensus development project の基準を診断に用いている施設は 11%，長期フォローの診療にマニュアルを作成している施設は 1%であった。構造的問題として医師・専従の看護師など人材の不足，診療プロセスの問題点では日本のガイドラインの充実や人材養成・教育の必要性などがあげられた。移植後の患者 QOL の向上には，長期フォローのための基盤整備と人材育成・資源配分が必要と考えられた。（臨床血液 **51**（3）：167～173，2010）

Key words : Long-term follow-up, Chronic GVHD, Stem cell transplantation

緒　言

近年，移植技術の向上により移植適応範囲は拡大し同種造血細胞移植数が増加している。現在では骨髄移植推進財団を介した非血縁同種骨髄移植だけでも年間 1,000 例に迫る勢いである[1]。しかし，同種移植は移植片生着後も長期に渡って合併症のマネジメントが必要であり[2]，移植後患者の生活の質を維持するためには，患者と共に医療スタッフの相当の努力を要する。

2005 年に NIH consensus development project on criteria for clinical trials in chronic GVHD（NIH 基準）が発表され[3~8]，慢性 GVHD の新しい診断基準と評価方法，効果判定基準などが示された[3~8]。また，2006 年 EBMT，CIBMTR および ASBMT により造血幹細胞移植後長期生存患者に対するスクリーニングと合併症予防に関する合同勧告が出された[9]。これらの基準や勧告では詳細かつ各臓器におよぶ定期スクリーニングが推奨されている。

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しかし，我が国の医療体制では，移植後長期生存患者に対する定期的かつ詳細なスクリーニングを実施することは必ずしも容易ではないと思われる。

本研究では，我が国における造血幹細胞移植後の慢性 GVHD や晩期障害などに対する長期フォローアップシステムについての実態を調査し，問題点の掘り起こしを試みた。

対象と方法

2008 年 6 月から 7 月にかけて，全国の移植施設に対して質問紙を用いた郵送による調査を施行した。

①研究対象

骨髄移植推進財団認定移植施設 194 施設における連絡責任医師と移植業務にたずさわる看護師。

②方法

質問紙を用いた郵送による調査

医師に対する調査内容は構造的問題として施設規模，造血幹細胞移植数，長期フォロー患者数，診療時間，関係各科との連携，多職種の関与，移植患者のために特化した外来枠の有無，長期フォローのための外来枠を設けているか否か。移植後長期フォローに関するクリニカルプロセスについて，診療指針，慢性 GVHD 診療に用いる基準，晩期合併症スクリーニングについて。自由記述にて今後の移植後長期フォローの在り方，移植専門外来の設置についての意見。など，多肢選択および自由記述

による半構成的質問紙を用いた。

その他，感染予防，慢性 GVHD の具体的治療内容についても質問項目を設けたが，今回の解析とは別に報告することとした。

看護師用の質問紙には，外来で長期フォロー患者のケア担当者について，外来で実施するケアの内容，病棟との連携など。自由記述については，医師用と同じ設問とした。

質問紙の妥当性を担保するために 2008 年 3 月から 4 月にかけて任意の 10 施設に対してプレテストを施行し，各設問に対する評価を行った上で修正を加え，全国の移植施設への調査を行った。

質問紙は，医師用と看護師用質問紙の 2 つを連絡責任医師へ一括送付し，回収は別々に行った。

本研究は，疫学研究に関する倫理指針（平成 16 年全部改訂）に則り実施された。倫理的配慮のため，回答のあった施設名・医師名等は非公開とした。

結　果

194 施設中，医師からの回答 100 施設（回収率 51.1%），看護師からの回答 71 施設（回収率 36.6%）であった。回答した看護師の所属部署は外来 9.8%，病棟 78.7%，病棟兼外来 3.3%，回答なし 8.2%であった。

Ⅰ．構成的設問に対する回答

〈構造的問題〉

回答のあった施設の規模は 500～1,000 床未満が最も多く，ついで 1,000 床以上，300～500 床未満であった。移植用ベッド数の中央値は 5 床（1～50 床）であった。

移植に携わる人的資源は，移植に携わる医師総数中央値 6 名（3～17 名），常勤医師数中央値 4 名（1～14 名），レジデント 1 名（0～6 名），非常勤医師 0 名であった。年間同種移植数の中央値は 10 例（0～57 例），非血縁骨髄移植 4 例（0～23 例）/年，血縁移植 3 例（0～45 例）/年，臍帯血移植 2 例（0～15 例）。定期的に外来でフォローしている移植後長期生存患者数は，50 名未満 50%，50～99 名 27.6%，100～300 未満 22.6%で，長期フォローの患者一人当たり診療時間は中央値 12.5 分（5～60 分）であった。診療時間について関連因子を解析したが，施設病床数，移植用病床数，移植に携わる医師数，造血幹細胞移植実施数，長期フォロー患者数のどの項目とも有意な相関はなかった。一人当たり 25 分以上かけて診療を行っている施設は 11 施設あり，医師数の中央値は 6 名（4～14 名），同種移植数 6 例（3～37 例）であった。

医師以外の職種が長期フォロー患者の診療へ関与している施設は 46.0%でその多くは看護師（33.0%）であり，医師以外の職種が関与しない施設は過半数（54.0%）であった。長期フォロー患者に 25 分以上の診療時間をかけている施設の 72.7%（11 施設中 8 施設）では医師以外の職種が診療に関与していた。

移植患者のために特化した外来枠を設けていると回答した施設は 5 施設（5%），また，移植後，長期フォローのための外来枠を設けていると回答した施設は 7 施設（7.0%）であった。長期フォロー患者に対して 25 分以上の診療時間をかけている施設は，移植患者のために特化した外来枠を設けている施設の 20.0%であったが，長期フォローのための外来枠を設けている施設では 57.1%であった。

〈晩期合併症の診療プロセス〉

採用している慢性 GVHD の診断基準について：NIH 基準を使用している施設 11.0%，発症時期を問わない慢性 GVHD 所見 64.0%，100 日以降の GVHD 所見としている施設は 23.0%であった。慢性 GVHD の重症度分類として実際の診療で用いている評価法について：NIH 基準を用いている施設は 5.0%，Limited または extensive の従来型の分類を用いている施設は 95.0%であった。治療効果判定の基準として NIH 基準を用いている施設は 11.0%であり，89.0%の施設では医師の経験に基づいた判定を行っていた（図 1）。

晩期合併症に関するスクリーニングの頻度：婦人科，消化器，乳がんなど移植後の患者でリスクが高まる癌に関して定期的にスクリーニングを実施している施設は 10%以下，心機能・呼吸機能など臓器機能についての定期検査実施施設は 50%未満であり，その他多くの施設では，何らかの症状が出現した際に検査を実施していると回答した（図 2）。

こうした移植後長期フォローの患者に対する診療について，施設でマニュアルを有していると答えた施設は 1.0%，マニュアルはないがコンセンサスに基づいて診療している施設は 24.0%，各医師の判断によると回答した施設 73.0%，その他 2.0%であった。

移植後長期フォロー患者のケアについて（看護師対象の調査結果）：外来でのケアを担当する職種は，看護師 47.1%，医師 17.6%，医師と看護師 5.9%，移植コーディネーター 2.9%，担当者なし 26.5%であった。外来でケアを担当する看護師のうち 60.0%が移植看護の経験者で 40.0%は移植看護未経験者であった。

移植後生活指導の担当職種は看護師 74.2%，医師と看護師 12.9%，医師のみで指導を行っている施設 6.5%，移植コーディネーター 1.6%，回答なし 4.8%であった。また，指導の担当者の所属は 78.7%が病棟に所属しており，外来所属 9.8%，病棟兼外来 3.3%，回答なし 8.2%であった。

移植後患者のケアについて病棟と外来の連携がある施設は 46.7%，連携がない施設 48.3%，回答なし 5.0%で