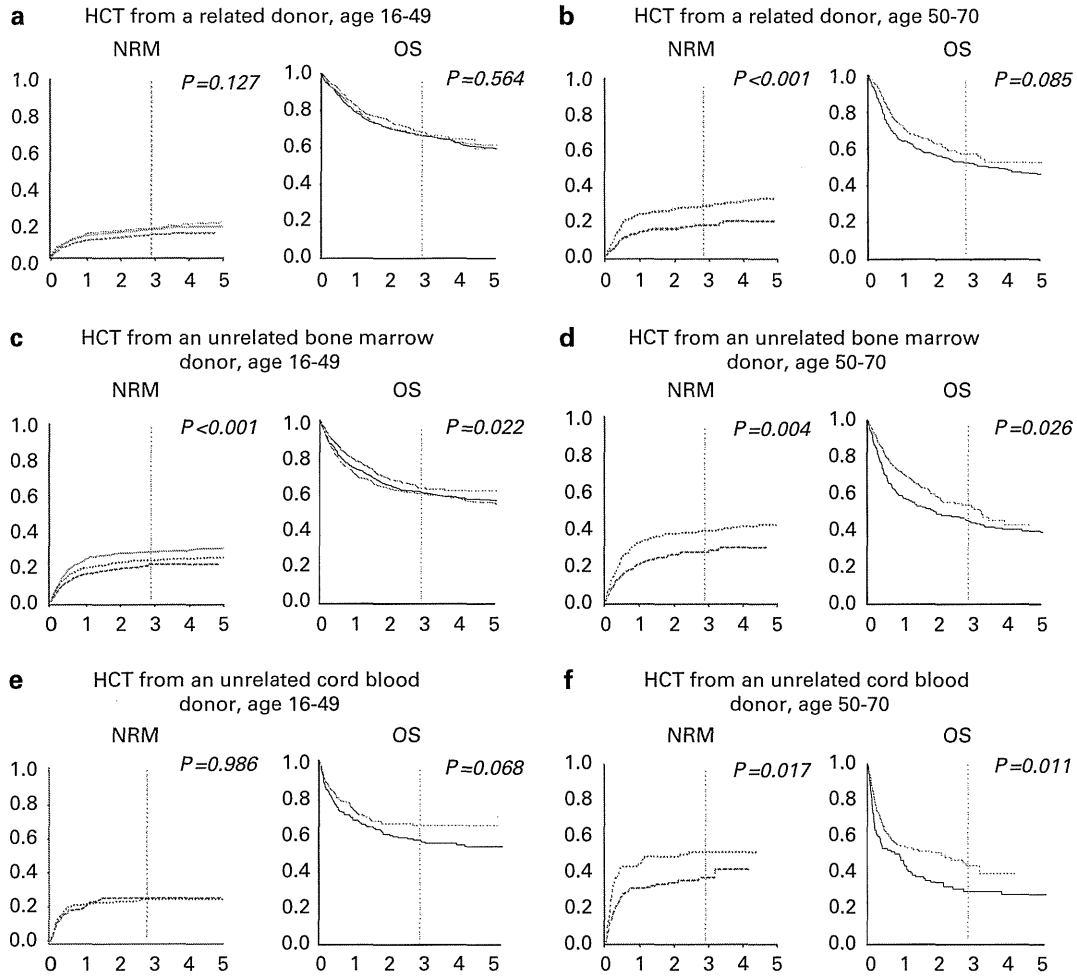

Figure 3. (**a**) NRM and OS at 3 years from HCT among younger patients (16–49 years) who received allo-HCT from a related donor were 15%, 16% and 12% ($P=0.127$), and 67%, 66% and 68% ($P=0.564$), respectively in the period of 1997–2000 ($n=587$, solid line), 2001–2004 ($n=620$, dotted line) and 2005-2008 ($n=639$, dashed line). (**b**) NRM and OS among older patients (50–70 years) who received related donor transplantation were 28% and 17% ($P<0.001$) and 52% and 57% ($P=0.085$), respectively in the period of 2001–2004 ($n=293$, dotted line) and 2005–2008 ($n=321$, dashed line). (**c**) NRM and OS among younger patients who received allo-HCT from an unrelated BM donor were 28%, 24% and 22% ($P<0.001$), and 60%, 60% and 63% ($P=0.022$), respectively in the period of 1997–2000 ($n=560$, solid line), 2001–2004 ($n=803$, dotted line) and 2005-2008 ($n=839$, dashed line). (**d**) NRM and OS among older patients who received allo-HCT from an unrelated BM donor were 39% and 27% ($P=0.004$) and 45% and 54% ($P=0.026$), respectively in the period of 2001–2004 ($n=195$, dotted line) and 2005–2008 ($n=473$, dashed line). (**e**) Non-relapse mortality and OS among younger patients who received allogeneic hematopoietic cell transplantation from an unrelated cord blood donor were 25% and 25% ($P=0.986$), and 55% and 65% ($P=0.068$), respectively in the period 2001–2004 ($n=214$, dotted line) and 2005–2008 ($n=292$, dashed line). (**f**) Non-relapse mortality and OS among older patients who received allogeneic hematopoietic cell transplantation from an unrelated cord blood donor were 51% and 37% ($P=0.017$), and 29% and 44% ($P=0.011$), respectively in the period of 2001–2004 ($n=107$, dotted line) and 2005–2008 ($n=242$, dashed line).

14 and 8%, $P=0.049$, Figure 4c). We found a significant reduction in mortality rates associated with bacterial and fungal infection.

Allo-HCT from an unrelated CB donor

In younger patients who received allo-HCT from an unrelated CB donor, there was no significant difference in the incidence of NRM between the two periods (Figure 3e). In this group, there was a marked reduction in the relapse rate (25 and 18%, $P=0.018$, data not shown; HR 0.66, 95% CI 0.43–1.00, $P=0.049$, Table 2). OS was better in 2005–2008; however, the difference was not statistically significant.

Significant improvements in NRM and OS were observed in 2005–2008 among older patients who received UCBT (Figure 3f). The HRs for NRM and overall mortality in 2005–2008 were 0.57 (95% CI 0.40–0.83, $P=0.003$) and 0.67 (95% CI 0.49–0.91, $P=0.010$), respectively. Reductions in the incidences of death associated with GVHD and infection seemed to contribute to the improvements in NRM (GVHD, 7 and 3%, $P=0.163$; infection, 23 and 13%, $P=0.136$). The mortality rate due to bacterial infection was significantly reduced.

Incidence of and mortality after severe acute GVHD

In subgroups that showed a significant reduction in the incidence of NRM, younger patients who received UBMT, older patients who received related HCT and older patients who received UCBT showed significant reductions in the incidence of GVHD-related mortality. In younger patients who received UBMT, the incidence of severe acute GVHD was significantly reduced over the three

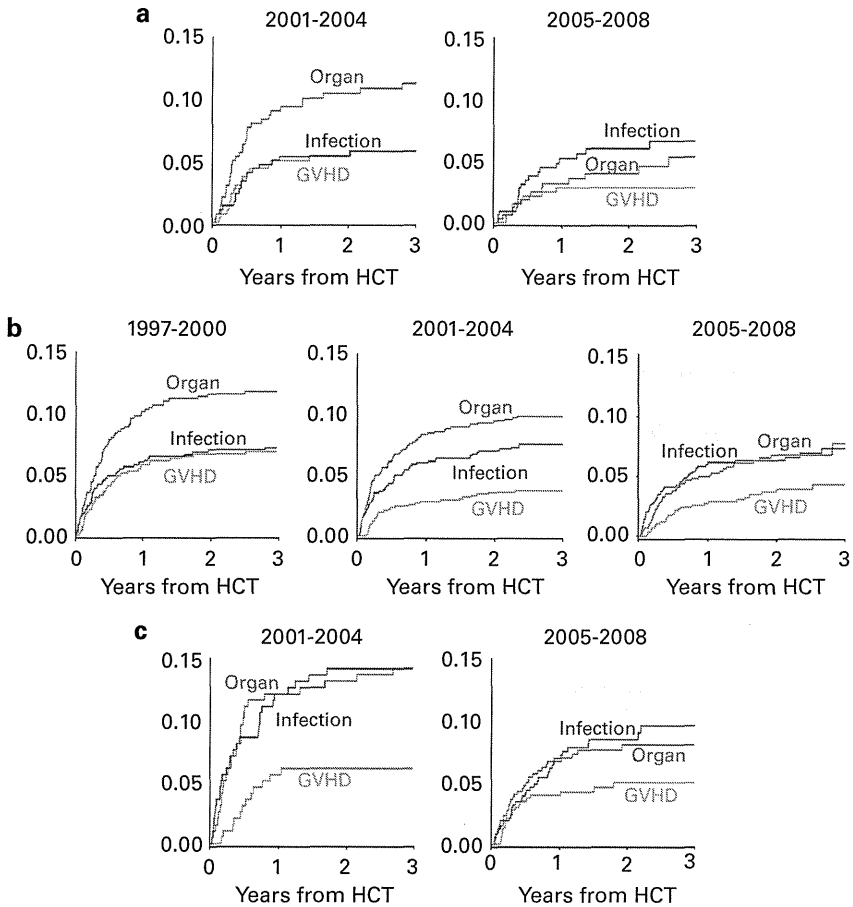

Figure 4. Change in the causes of NRM among different time periods is shown. Cumulative incidences of death due to GVHD, infection and organ failure are separately presented in each time period. (**a**) In older patients who received allo-HCT from a related donor, the incidences of death associated with organ failure and GVHD were significantly reduced in 2005–2008 (organ failure, 11 and 6%, $P=0.007$; GVHD, 6 and 3%, $P=0.015$). (**b**) In younger patients who received allo-HCT from an unrelated BM donor, the incidences of death associated with GVHD and organ failure were significantly reduced (GVHD, 7, 4 and 4%, $P=0.011$; organ failure, 12, 10 and 8%, $P=0.002$). (**c**) In older patients who received allo-HCT from an unrelated BM donor, the incidences of death associated with infection and organ failure were reduced in 2005–2008 (infection, 14 and 10%, $P=0.054$; organ failure, 14 and 8%, $P=0.049$).

periods (16, 15 and 12% at 100 days after allo-HCT, $P=0.021$). In older patients who received related HCT, the incidence of severe acute GVHD was reduced in 2005–2008 relative to 2001–2004, but this difference was not statistically significant (14 and 10%, $P=0.099$). In older patients who received UCBT, there was no remarkable reduction in the incidence of severe acute GVHD in the later period (18 and 16%, $P=0.542$). However, the mortality rate was significantly reduced among older patients who suffered severe acute GVHD after UCBT (92 and 67% at 3 years after allo-HCT, $P=0.022$).

DISCUSSION

In this study that used a large database of 6501 patients, we found that the incidence of NRM after allo-HCT for adult patients has significantly decreased over the past 12 years, which has led to an improvement of OS. As prior studies have primarily focused on the changes in NRM among younger patients who received allo-HCT with myeloablative conditioning,[2,4] this is the first study to show the changes in NRM in subgroups comprising older patients and UCBT.

We found that demographic, disease and transplantation characteristics have been changing, as previous studies reported.[1,2,4] The marked increase in the number of older patients, allo-HCT with reduced-intensity conditioning and UCBT might reflect an increase in allo-HCT for 'more vulnerable' patients. Gooley *et al.*[1] reported that the hematopoietic cell transplantation-specific comorbidity index (HCT-CI)[7] scores were higher in HCT recipients in more recent time periods. Unfortunately, we were not able to evaluate HCT-CI in the current study because of a lack of information.

Among patients who received related HCT, remarkable improvement in NRM was observed in older patients. Another distinguishing finding was an increase in relapse in overall older patients, especially among those who received related HCT in remission. There was no recent shift in the use of allo-HCT in a later remission state, and we obtained a similar result when the analyses were restricted to HCT using reduced-intensity regimens or myeloablative regimens. In addition, the proportional use of anti-thymocyte globulin has remained unchanged over the periods. Less use of PB donors and more aggressive selection of older patients as indicated for allo-HCT may have affected the result. Despite this increase in relapse, older patients who received HCT in remission showed, by multivariate analyses, a significant reduction in mortality with a remarkable reduction in HRs for NRM irrespective of donor sources.

In analyses based on the donor source, UBMT showed remarkable improvements in NRM and OS throughout the age subgroups. Along with high-resolution donor–recipient HLA

matching,[8,9] the lesser proportion of donor/patient pairs with allele mismatches may have reduced the incidence of GVHD-related mortality, and contributed to the improvement in outcomes after UBMT.

Among patients who received UCBT, we found a decreased risk of relapse in younger patients with no change in NRM. On the other hand, older patients had a decreased risk of NRM with no change in relapse. These outcomes may be explained by the changes in clinical practice in 2001–2004, 'learning phase' of UCBT, and that after 2005, including the indication of UCBT and the prophylaxis and treatment for GVHD/infection.

A recent reduction in the incidence of GVHD-related mortality was observed in younger patients receiving UBMT and older patients receiving related allo-HCT or UCBT. With the changes in prophylaxis and treatment against GVHD including high-resolution donor–recipient HLA matching,[8,9] the incidence of grade 3 to 4 severe acute GVHD has decreased in younger patients receiving UBMT and older patients receiving related HCT, which may have led to the reduction in GVHD-related mortality in these subgroups. Interestingly, in older patients receiving UCBT, there was no reduction in the incidence of severe acute GVHD; however, the mortality rate among those who developed severe acute GVHD was reduced. The prompt initiation of treatment after a more thorough examination to diagnose GVHD,[10] supportive care and nutritional management may have improved the prognosis of those who had severe GVHD. Alternatively, the unique HLA epidemiological genetics of Japanese patients may have affected the results.[11,12]

A recent reduction in the incidence of infection-related mortality was observed in older patients receiving UBMT or UCBT. New antifungal drugs, including mold-active azoles, micafungin or liposomal amphotericin B, are now more likely to be administered as empiric or preemptive strategies for patients who have a positive galactomannan Ag test or pulmonary nodules.[1,13,14] As GVHD and infection have been reported to be associated with each other's development and exacerbation,[13,15–18] an improved control of severe GVHD may have led to the reduction of the risk of infection-related mortality.[13,14]

We included all of the organ toxicities that were documented after allo-HCT as the cause of organ failure-related mortality, including conditioning regimen-related toxicity,[19,20] lung injury[15] and late effects on any organs.[21] We observed a reduction in the incidence of organ failure-related mortality in older patients receiving related HCT and those who received UBMT. In the future, more detailed analyses are warranted based on each specific organ toxicity.

As this analysis is based on a retrospectively collected multicenter database, our results may be susceptible to the disadvantages of any retrospective study, such as the heterogeneity in the treatment strategies chosen at the discretion of the physicians. Because of the nature of the multicenter registry, detailed data were not available regarding the incidences of infection and specific organ failure, and prophylactic treatment toward infection. Although we acknowledge this limitation, the results obtained from this large database that contains clinical data on over 6000 patients should provide valuable information. In addition, for the first time, we found reductions in NRM in subgroups consisting of older patients and those who received UCBT. We also showed the causes of death that contributed to the reduction of NRM in each donor/age subgroup. By further evaluating the risks of NRM and relapse in each demographic subgroup, we would be able to more clearly define the indications for allo-HCT, and tailor the strategy for individual patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Stenotrophomonas maltophilia infection in hematopoietic SCT recipients: high mortality due to pulmonary hemorrhage

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To clarify the clinical features and outcome of *Stenotrophomonas maltophilia* infection among hematopoietic SCT (HCT) recipients, we retrospectively reviewed the records of 1085 consecutive HCT recipients and identified 42 episodes in 31 HCT recipients with *S. maltophilia* infection. We compared these recipients with 30 non-HCT patients with *S. maltophilia* infection. The mortality rate in HCT recipients was significantly higher than that in non-HCT patients (relative risk 5.7, $P=0.04$), and we identified seven patients with pulmonary hemorrhage due to *S. maltophilia*, exclusively in the HCT cohort. Six of these latter seven patients died within 1 day from the onset of hemorrhage and the isolate was identified after death in most cases; one patient, who received empiric therapy for *S. maltophilia* and granulocyte transfusion, survived for more than 2 weeks. The patients with pulmonary hemorrhage had a more severe and longer duration of neutropenia, persistent fever despite of the use of broad-spectrum antibiotics, complication by pneumonia and higher C-reactive protein levels than those without pulmonary hemorrhage. In conclusion, *S. maltophilia* was associated with fulminant and fatal pulmonary hemorrhage in HCT recipients. Empiric therapy with antibiotics before the onset of pulmonary hemorrhage may be effective in HCT recipients who carry the conditions identified.

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Keywords: *Stenotrophomonas maltophilia*; SCT; pulmonary hemorrhage

INTRODUCTION

Stenotrophomonas maltophilia is a non-fermentative, Gram-negative bacillus that is ubiquitous in the natural and hospital environment,[1–4] and exhibits intrinsic resistance to many antibiotics including β-lactams, carbapenems and aminoglycosides.[5,6] Although *S. maltophilia* is not usually highly virulent, it is a significant pathogen in immune-compromised patients, and the incidence of *S. maltophilia* infection is increasing.[7]

Previously, in a heterogeneous group that included recipients of hematopoietic SCT (HCT) and non-HCT patients with solid tumor or hematological malignancy, risk factors for acquiring *S. maltophilia* infection were reported to be prolonged neutropenia, exposure to broad-spectrum antibiotics, mucositis, indwelling medical devices such as an intravascular catheter or ventilation tubes and long hospital stays.[8–12] In a similarly heterogeneous group, risk factors for mortality of *S. maltophilia* infection were reported to be neutropenia, hematological malignancy, immunosuppressive therapy, shock status at infection onset and intensive-care unit stays.[13–17] However, only limited information is available on HCT recipients.[12,18,19] Many of the previously reported risk factors are commonly seen in HCT recipients because of their severe immunosuppressive status and mucositis due to preparative conditioning and immunosuppressive therapy for GVHD prophylaxis.

Hence, *S. maltophilia* infection in HCT recipients may have a different spectrum and greater severity compared with that in patients with solid tumor or non-HCT setting hematological malignancy. To clarify the clinical features and outcome of *S. maltophilia* infection with a particular focus on HCT recipients, we retrospectively analyzed clinical data on patients who had *S. maltophilia* infection.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the medical and microbiological records of all the HCT recipients at the National Cancer Center Hospital (Tokyo, Japan) between January 2001 and December 2010, and identified episodes of *S. maltophilia* blood stream infection (BSI) among the HCT recipients. We also reviewed the medical and microbiological records of all patients whose blood cultures were positive for *S. maltophilia* at our institution in the same period and identified episodes of *S. maltophilia* BSI among the non-HCT patients. We then compared the clinical features and outcomes in the HCT cohort with those in the non-HCT control cohort.

Definitions

An episode of *S. maltophilia* BSI was defined as one or more positive blood cultures for *S. maltophilia* with clinical signs of infection. When *S. maltophilia* was again detected in the same patient at an interval of 8 or more days after the first BSI episode had improved, the detection of the isolate was regarded as a different episode of BSI, as previously reported.[13,20] The severity of illness was assessed by the bacteremia score according to the University of Pittsburgh (PITT score).[21,22] The D-index and cumulative D-index, which were calculated as the area over the neutrophil curve that is based on a graph plotting the absolute neutrophil counts during neutropenia,[23] were also investigated to evaluate the impact of both duration and severity of neutropenia on *S. maltophilia* infection.

Infection control in HCT recipients and microbiological investigations

Among the HCT recipients, prophylaxis for infection consisted of trimethoprim-sulfamethoxazole (ST), ciprofloxacin, fluconazole and acyclovir. As therapy for febrile neutropenia, cefepim was first administered in

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most cases, and in cases that did not improve within 2–3 days, either it was switched to carbapenem or vancomycin was added.

Two sets of blood culture samples from a double-lumen intravascular catheter and another from peripheral blood were routinely taken at the initial episode of fever. If fever persisted, one set of the blood culture samples was taken daily from either the lumen of the intravascular catheter or a peripheral vessel alternately. Blood culture samples were processed using a BACTEC 9240 (before 2008) or BACTEC FX (after 2009) system (Becton Dickinson Microbiology Systems, Sparks, MD, USA). Susceptibility to antibiotics was tested by the broth microdilution method according to the guidelines of the National Committee for Clinical Laboratory Standards.

Statistical analysis

The end point was defined as death within 4 weeks from the onset of a positive blood culture for *S. maltophilia*. Categorical variables were analyzed using a Chi-squared test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann–Whitney *U*-test. To investigate risk factors for death within 4 weeks in all cases including both HCT and non-HCT cases, a multivariate logistic regression analysis was performed. The following factors were used as covariates: age (<45 vs $\geqslant 45$ y), severe neutropenia at BSI onset, PITT score ($\leqslant 1$ vs >1), complication by pneumonia and therapy for underlying disease (HCT vs non-HCT). The statistical analysis was performed with the SPSS 11.0 statistical software package (SPSS Inc, Tokyo, Japan).

RESULTS

Patient characteristics

In the study period between 2001 and 2010, a total of 1085 HCT (847 allogeneic HCT and 238 autologous HCT) procedures were performed in our institution. A total of 42 episodes (35 episodes in allogeneic HCT recipients and 7 episodes in autologous HCT recipients) of *S. maltophilia* BSI were identified in 31 HCT recipients (2.9%). There was no obvious outbreak of *S. maltophilia* infection in the study period.

The patient characteristics are shown in Table 1. Broad-spectrum cefem or carbapenem was administered in 60% of the episodes at BSI onset. With regard to the therapy for *S. maltophilia* infection, the intravascular catheter was removed in 10 (24%) episodes in which catheter-related BSI was suspected. When *S. maltophilia* BSI was diagnosed, ST or fluoroquinolone was started based on the susceptibility test in 19 episodes, whereas no antibiotics were additionally administered in 7 episodes where *S. maltophilia* was only detected in blood culture after death.

Clinical outcome

In all, 14 patients died within 4 weeks from the onset of a positive blood culture for *S. maltophilia*. We divided causes of death into two patterns; eight patients were judged to have died from a single cause due to *S. maltophilia* infection, whereas six appeared to have died of complex causes, which consisted of *S. maltophilia* infection and some other cause (underlying disease progression in two, GVHD in two, other infection in one and suffocation due to vomiting in one). Pulmonary hemorrhage accounted for half of the 14 deaths. Among the 847 allogeneic HCT recipients, 18 patients (2.1%) developed pulmonary hemorrhage (infection of *S. maltophilia*: $n=7$, Aspergillus species: $n=3$, *Pseudomonas aeruginosa*: $n=1$, Staphylococcus species: $n=1$, cytomegalovirus: $n=1$, idiopathic pneumonia syndrome/diffuse alveolar hemorrhage: $n=2$, disseminated intravascular coagulation: $n=1$, tumor invasion: $n=1$ and unknown cause: $n=1$).

Seven cases with pulmonary hemorrhage

The details of the seven patients with pulmonary hemorrhage are shown in Table 2. All the episodes of pulmonary hemorrhage occurred during a period of profound neutropenia (neutrophil count 0/μL).

Table 1. Patients and clinical characteristics of HCT recipients who developed *S. maltophilia* BSI

	Total 31 patients (42 episodes)	*%*
Age, median, range	44 years, 4–67 (43 years, 4–67)	
Sex (male/female)	25/6 (34/7)	81/19 (81/19)
Underlying disease		
Leukemia	19 (24)	61 (57)
Lymphoma	7 (9)	23 (21)
MDS/myelofibrosis	3 (3)	10 (7)
Solid tumor	2 (6)	6 (14)
Type of HCT		
Allogeneic	28 (35)	90 (83)
Autologous	3 (7)	10 (17)
Conditioning for allo-HCT		
Myeloablative	15 (19)	54 (54)
Reduced intensity	13 (16)	46 (46)
Donor and source		
Related PB	8 (9)	26 (21)
Related BM	1 (1)	3 (2)
Unrelated BM	14 (18)	45 (43)
Cord blood	5 (7)	16 (17)
Autologous PB	3 (7)	10 (17)
Immunosuppressive agents		
CSP ± steroid	13 (16)	42 (38)
TAC ± steroid	9 (11)	29 (26)
Steroid	4 (4)	13 (10)
None	5 (11)	16 (26)
CV indwelling	30 (41)	97 (98)
Antibiotics at BSI onset		
Carbapenem ± vancomycin	13 (18)	42 (43)
Broad cefem or penicillin	6 (7)	19 (17)
Ciprofloxacin (prophylaxis)	8 (9)	26 (21)
ST (prophylaxis)	2 (4)	6 (10)
Other	1 (1)	3 (2)
None	1 (3)	1 (7)
Therapy for infection		
CV removal	7 (10)	23 (24)
Granulocyte Transfusion	2 (2)	6 (5)
ST	5 (5)	16 (12)
ST + quinolone	3 (3)	10 (7)
ST + ceftazidime	1 (2)	3 (5)
Quinolone ± minocyclin	7 (9)	23 (21)
Ceftazidime	3 (4)	10 (7)
None	9 (9)	29 (21)

Abbreviations: BSI = blood stream infection; CSP = cyclosporine; CV = central venous catheter; HCT = hematopoietic SCT; MDS = myelodysplastic syndrome; PB = peripheral blood; ST = trimethoprim-sulfamethoxazole; TAC = tacrolimus.

As initial symptoms, all patients showed persistent fever that did not respond to broad-spectrum antibiotics. Other symptoms included chest pain ($n=4$), back pain ($n=2$), hemosputum ($n=2$) or dyspnea ($n=1$). Imaging test findings of chest X-ray ($n=5$) or computed tomography ($n=5$) in all patients showed consolidation that was consistent with symptoms such as chest pain. Six patients (cases 1–3 and 5–7) developed massive hemoptysis within 1–4 days after the initial chest symptoms. At the onset of massive hemoptysis, all the patients developed respiratory and circulatory failure due to bleeding and sepsis. Six patients, but not case 7, died within 1 day after hemoptysis.

Table 2. Details of patients with pulmonary hemorrhage due to *S. maltophilia*

Case	Age/ gender	Underlying disease	Type of HCT	Conditioning	Onset day[a] of hemorrhage	Day[a] of death	Day[a] of identification of S maltophilia		Treatment for S maltophilia infection
							Sputum	Blood	
1	27/M	AML	CBT	CA + CY + TBI 12 Gy	10	10	After death	After death	None
2	37/M	Myelofibrosis	U-BMT	BU + CY	11	11	After death	After death	None
3	54/M	AML	U-BMT	CY + TBI 12 Gy	15	16	12	After death	None
4	58/M	AML	CBT (second allogeneic HCT)	Flu + BU + TBI 2 Gy	18	18	9	After death	CAZ
5	43/M	AML	CBT (second allogeneic HCT)	Flu + Mel	6	7	Previously known	After death	ST + PZFX + CAZ
6	24/M	AML	R-PBSCT	BU + CY	445 (11)[b]	446 (12)[b]	NA	445 (11)[b]	ST
7	51/M	AML	U-BMT	BU + CY	39	55	42	40	ST + PZFX granulocyte transfusion

Abbreviations: CA = cytarabine; CAZ = ceftazidime; CBT = cord blood transplantation; Flu = fludarabine; HCT = hematopoietic SCT; Mel = melpharan; NA = not assessment; PZFX = pazufloxacin; R-PBSCT = related PBSCT; ST = trimethoprim-sulfamethoxazole; U-BMT = unrelated BMT. [a]Day after allogeneic HCT. [b]Day after chemotherapy using idarubicin and cytarabine for relapse after allogeneic HCT.

Because of the significantly rapid clinical course, *S. maltophilia* was detected in blood culture after death or 1 day before death in six patients (cases 1–6) and, similarly, *S. maltophilia* was detected in sputum culture after death in two patients (case 1 and 2).

Therapy for *S. maltophilia* was not initiated in three cases (cases 1–3) because the isolate was identified after death. In case 7, the administration of ST and pazufloxacin was started before the onset of hemoptysis and the identification of isolate because pulmonary hemorrhage due to *S. maltophilia* was suspected based on a typical clinical course and imaging test findings. Granulocyte transfusion was also started 38 h after the onset of hemoptysis and 28 h after the detection of *S. maltophilia* in blood culture. This patient survived for 16 and 15 days after the onset of hemoptysis and the identification of BSI, respectively. However, he eventually died due to *S. maltophilia* infection associated with primary graft failure. In case 5, the administration of ST and pazufloxacin was started before hemoptysis because he had a past history of *S. maltophilia* infection. The isolates exhibited resistance to the antibiotics used and he died within 1 day after hemoptysis. Bronchial arterial embolization was performed for pulmonary hemorrhage in two patients (case 1 and 5), however, neither were rescued.

Pulmonary hemorrhage due to *S. maltophilia* was diagnosed by the detection of *S. maltophilia* in blood and sputum cultures, histopathological findings of pulmonary hemorrhage and the presence of massive infiltration of Gram-negative rods in lungs by autopsy in three cases (cases 2, 3 and 5) (Figure 1). Cases 1 and 7 were diagnosed by the detection of *S. maltophilia* in blood and sputum cultures and the confirmation of pulmonary hemorrhage using bronchoscopy. Case 4 was diagnosed by the detection of *S. maltophilia* in blood and sputum cultures and clinical symptoms such as hemoptysis. Case 6 was diagnosed by the detection of *S. maltophilia* in blood culture and pulmonary hemorrhage confirmed by bronchoscopy.

Although the histopathological findings at autopsy in case 2 demonstrated one focal small nodule of aspergillosis in the right upper lobe, pulmonary hemorrhage was mainly found in the bilateral lower lobes, and therefore was mainly assumed to be due to *S. maltophilia* infection. There was no histopathological evidence of fungal infection in the other autopsy cases. Serum galactomannan Ag and β-D-glucan were tested at around the onset of pulmonary hemorrhage and results were negative in six cases, but not in case 2. The clinical characteristics and outcome in patients with and without pulmonary hemorrhage are compared in Table 3. Patients with pulmonary hemorrhage were associated with severe and longer duration of neutropenia, higher C-reactive protein levels at BSI onset, a higher D- and cumulative D-index, a higher incidence of complication by pneumonia and higher mortality than those without pulmonary hemorrhage.

Comparison of HCT recipients with non-HCT patients

The clinical characteristics and outcomes of HCT recipients (42 episodes) were compared with those of 30 non-HCT patients (15 episodes with hematological malignancy and 15 with solid tumor) who developed *S. maltophilia* infection (Table 3). HCT recipients were more likely to be associated with severe neutropenia (<100/μL), use of immunosuppressive agents and a higher mortality within 4 weeks after *S. maltophilia* BSI than non-HCT patients.

Although there was no significant difference in the proportion of patients with *S. maltophilia* pneumonia between the HCT recipients and non-HCT patients, pulmonary hemorrhage was seen only in HCT recipients. By a multivariate analysis in all the 72 episodes, including both HCT ($n = 42$) and non-HCT cases ($n = 30$), the independent risk factors for mortality within 4 weeks after *S. maltophilia* BSI were HCT recipient (relative risk 5.7, 95% confidence interval 1.1–30.1, $P = 0.04$) and complication by pneumonia (relative risk 10.7, 95% confidence interval 2.6–44.2, $P = 0.001$).

Susceptibility of strains of *S. maltophilia* from HCT recipients

A total of 41 strains of *S. maltophilia* isolated from HCT recipients were tested with regard to their susceptibility to antibiotics. The percentages of isolates that were susceptible to ST (81%), minocycline (93%) and levofloxacin (68%) were relatively high, whereas fewer isolates were susceptible to ceftazidime (26%), amikacin (21%), cefepime (5%) and imipenem (3%). There were no significant differences in susceptibility to each antibiotic between isolates from HCT recipients and those from non-HCT patients.

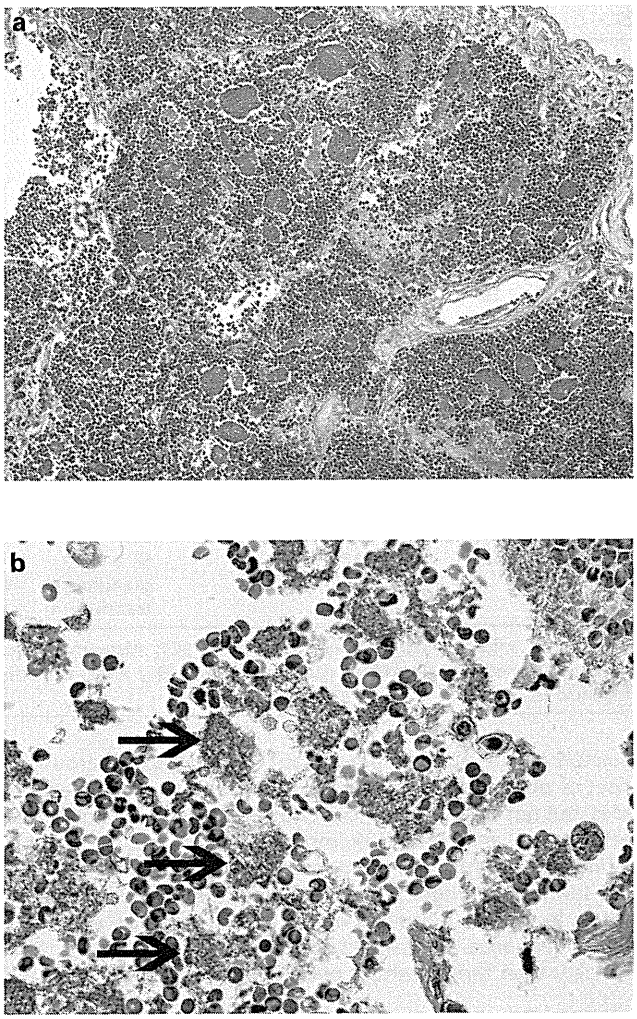

Figure 1. Lung section from case 5 (autopsy). (**a**) Massive intraalveolar hemorrhage and disseminated foci of basophilic bacteria (hematoxylin and eosin stain, × 40). (**b**) Higher magnification of hematoxylin and eosin staining showed a striking number of basophilic bacilli (arrow) without infiltration of the alveoli neutrophils and lymphocytes (× 400).

DISCUSSION

This is a retrospective study reporting the clinical characteristics and outcomes of *S. maltophilia* infection with a particular focus on HCT recipients. Our data revealed that HCT recipients who had *S. maltophilia* infection were more likely to be associated with pulmonary hemorrhage, which was the main cause of death in the cohort, and had a higher mortality within 4 weeks after *S. maltophilia* BSI than non-HCT patients.

Previous studies of *S. maltophilia* infection in HCT recipients included many patients with catheter-related BSI and emphasized the removal of an intravascular catheter and the administration of appropriate antibiotics according to the results of a susceptibility test.[13,18,19] Our results were consistent with those of previous studies because 28 out of 42 episodes (67%) of *S. maltophilia* infection in this study were successfully treated. However, in previous reports that included *S. maltophilia* infection in HCT recipients, there was no information on pulmonary hemorrhage due to *S. maltophilia*.[13,18,19] Additionally, in previous large studies of post-transplant pulmonary hemorrhage, *S. maltophilia* had not been detected as a cause of pulmonary hemorrhage.[24–26] There have been only a few reported cases in a non-HCT setting that were associated with pulmonary hemorrhage due to *S. maltophilia* after intensive chemotherapy against hematological malignancy.[27–30] Hence, this is the first report to comprehensively describe the overall picture of pulmonary hemorrhage due to *S. maltophilia* with a particular focus on HCT recipients, including the histopathological findings of autopsy, incidence, typical clinical course, risk factors and outcome.

By reviewing the medical records in detail, we identified the clinical characteristics of post-transplant pulmonary hemorrhage due to *S. maltophilia*. Risk factors for pulmonary hemorrhage due to *S. maltophilia* were HCT recipient, prolonged days of neutropenia, high C-reactive protein level at BSI onset and complication by pneumonia. In addition to the duration of neutropenia, the D- and cumulative D-index[23] were also considered to be factors that predicted pulmonary hemorrhage, whereas a high PITT score at the onset of BSI was not associated with pulmonary hemorrhage.

Typical findings that were recognized before pulmonary hemorrhage were persistent fever despite of the use of broad-spectrum antibiotics, chest symptoms, such as chest pain, and apparent consolidation in imaging test. In many cases, it was impossible to start antibiotic therapy based on the identification of *S. maltophilia* infection in blood or sputum culture because most patients developed a very aggressive clinical course and died before the *S. maltophilia* infection was detected. Hence, *S. maltophilia* infection should be predicted in the HCT recipients based on the presence of risk factors for pulmonary hemorrhage due to *S. maltophilia*, and treatment for *S. maltophilia* infection should be considered before hemoptysis occurs.

In one of our cases (case 7 in Table 2), *S. maltophilia* infection was suspected based on typical findings and risk factors for pulmonary hemorrhage due to *S. maltophilia*, and empiric therapy that consisted of ST and pazufloxacin was started before hemoptysis and the detection of isolate. Granulocyte transfusion was also started, which resulted in a long survival after pulmonary hemorrhage was observed. This case suggests that empiric therapy for *S. maltophilia* infection might be useful if typical findings appear in HCT recipients who have risk factors for pulmonary hemorrhage due to *S. maltophilia*.

Current treatment recommendations for antibiotics against *S. maltophilia* are based on historical evidence, case series, case reports and *in vitro* susceptibility tests because of the lack of controlled trials.[1,6] In general, ST has been shown to have the most potent and reliable *in vitro* activity against *S. maltophilia*, and alternate agents are new fluoroquinolone, tigecycline and ticarcillin–clavulanate. The isolates from both HCT recipients and non-HCT patients in our study were confirmed to have a high *in vitro* susceptibility to ST and new fluoroquinolone, however, tigecycline and ticarcillin–clavulanate were not tested because these drugs have not yet been approved in our country. Hence, ST alone or in combination with other susceptible agents is considered to be the treatment of choice for suspected or culture-proven *S. maltophilia* infection in HCT recipients. However, the myelotoxicity of ST might be a concern in the setting of HCT before engraftment.

The mechanism of *S. maltophilia*-induced pulmonary hemorrhage remains uncertain. *In vitro* data demonstrated that *S. maltophilia* produces proteases, which can break down the protein components of collagen, fibronectin and fibrinogen,[31,32] and this may contribute to local tissue damage and hemorrhage.[1] Because our present histopathological findings at autopsy demonstrated alveolar hemorrhage and the massive infiltration of Gram-negative rods in lungs without invasion by neutrophils or lymphocytes, *S. maltophilia* itself might damage lung tissue, which leads to pulmonary hemorrhage. In an HCT recipient with a highly immunosuppressive background, it is speculated that *S. maltophilia* infects and proliferates in lung tissue, which is fragile due to chemotherapy or TBI as a preparative conditioning, and thus leads to pulmonary hemorrhage with a coexisting tendency for

Table 3. Comparison of clinical characteristics and outcomes

	HCT cohort without pulmonary hemorrhage n = 35 (%)	*HCT cohort with pulmonary hemorrhage n = 7 (%)*	P	*HCT cohort n = 42 (%)*	*Non-HCT cohort n = 30 (%)*	P
Age, median, range	44, 4–67	43, 24–58	0.7	44, 4–67	49, 4–78	0.1
CRP (mg/dL) at BSI onset, median, range	3.0, 0.2–30.3	25.4, 5–31.2	0.001	4.9, 0.2–31.2	5.3, 0.5–23.4	0.9
Neutropenia (<500/μL) at BSI onset	20 (57)	7 (100)	0.04	27 (64)	13 (43)	0.08
Profound neutropenia (<100/μL) at BSI onset	19 (54)	7 (100)	0.03	26 (62)	10 (33)	0.02
Total days of neutropenia[a], median, range	4, 0–143	25, 6–143	0.02	7, 0–143	0, 0–92	0.09
Total days of profound neutropenia[a], median, range	2, 0–133	12, 4–133	0.02	4, 0–133	0, 0-84	0.05
D-index, median, range	1550, 0-70070	10400, 2600-70070	0.02	2950, 0-70070	0, 0-44400	0.09
Cumulative D-index, median, range	125, 0-46570	8400, 2600-64570	0.006	1550, 0-64570	0, 0-30200	0.08
PITT score >1	3 (9)	7 (100)	0.2	10 (17)	7 (23)	0.8
Coinfection	6 (17)	2 (29)	0.4	8 (19)	5 (17)	0.9
Use of immunosuppressive agents	24 (69)	7 (100)	0.2	31 (74)	2 (7)	<0.001
Pneumonia	10 (29)	7 (100)	0.001	17 (40)	9 (30)	0.4
Pulmonary hemorrhage	–	–	–	7 (17)	0 (0)	0.02
Death within 4 weeks	7 (20)	7 (100)	<0.001	14 (33)	3 (10)	0.02

Abbreviations: BSI = blood stream infection; CRP = C-reactive protein; HCT = hematopoietic SCT. [a]Day from onset of neutropenia (<500/μL) or profound neutropenia (<100/μL) to recovery of neutropenia or profound neutropenia. If a patient died without recovery of neutropenia, days of neutropenia or profound neutropenia were counted until the day of mortality.

bleeding due to a low platelet count and coagulation disorder. Further molecular microbiological studies are warranted to clarify the mechanism of *S. maltophilia*-induced pulmonary hemorrhage.

Our results also showed that most patients who died without pulmonary hemorrhage had complex causes of death, such as underlying disease progression or uncontrolled GVHD in addition to *S. maltophilia* infection. This might be due to the fact that infections due to *S. maltophilia* occur often in patients in poor condition.

Our study has some limitations; it includes a relatively small number of patients in a single institution and uses a retrospective study design. However, this is the largest study to focus on *S. maltophilia* infection in HCT recipients and is the first study to report the significance of pulmonary hemorrhage as a cause of death.

In conclusion, we showed that *S. maltophilia* infection in HCT recipients is associated with higher mortality than that in non-HCT patients, and causes fulminant and fatal pulmonary hemorrhage, which is a main cause of death in HCT recipients with *S. maltophilia* infection. We also showed that patients with pulmonary hemorrhage were associated with persistent fever despite of the use of broad-spectrum antibiotics, complication by pneumonia, severe and significantly longer duration of neutropenia and higher C-reactive protein levels at the onset of BSI than those without pulmonary hemorrhage. Empiric therapy before the onset of pulmonary hemorrhage may be effective in HCT recipients who exhibit these identified conditions because most patients with pulmonary hemorrhage due to *S. maltophilia* die within a short period without the detection of infection. Multicenter prospective or retrospective studies that focus on HCT recipients are warranted to evaluate the optimum therapeutic strategy against this fatal and intrinsic multidrug-resistant microbe.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Prognosis of acute myeloid leukemia harboring monosomal karyotype in patients treated with or without allogeneic hematopoietic cell transplantation after achieving complete remission

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ABSTRACT

To evaluate the prognostic impact of monosomal karyotype on post-remission outcome in acute myeloid leukemia, we retrospectively analyzed 2,099 patients who had achieved complete remission. Monosomal karyotype was noted in 73 patients (4%). Of these, the probability of overall survival from first complete remission was 14% at four years, which was significantly lower than that reported in patients without monosomal karyotype, primarily due to a high relapse rate (86%). Monosomal karyotype remained significantly associated with worse overall survival among patients with unfavorable cytogenetics or complex karyotype, and even in patients who underwent allogeneic hematopoietic cell transplantation during first complete remission. These findings confirm that monosomal karyotype has a significantly adverse effect on post-remission outcome in patients with acute myeloid leukemia treated with and without allogeneic hematopoietic cell transplantation in first complete remission, emphasizing the need for the development of alternative therapies for this patient population.

Key words: acute myeloid leukemia, monosomal karyotype, cytogenetics, post-remission therapy, allogeneic hematopoietic cell transplantation.

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease that includes subsets with distinct biological, clinical and prognostic features. It has been well established that cytogenetic abnormalities at diagnosis are associated with the biology of the disease and have important prognostic implications.[1-3] The coexistence of multiple cytogenetic abnormalities designated as complex karyotype (CK) has been recognized as a factor that predicts an extremely unfavorable outcome in AML.[4-7] However, the prognostic significance of CK has recently been challenged by Breems *et al.* who showed that the monosomal karyotype (MK), defined as 2 or more distinct autosomal monosomies or a single autosomal monosomy in the presence of other structural abnormalities, adversely affects the prognosis, and that the overlap of MK with CK is the main contributor to the unfavorable impact of CK.[8] According to Breems *et al.* and reports published subsequently by other groups,[7-10] patients with MK$^+$ AML show low complete remission (CR) rates ranging from 18% to 48% and overall survival (OS) rates of less than 10%. On the other hand, it has been suggested that such a poor outcome may be improved by allogeneic hematopoietic cell transplantation (HCT).[11]

To further clarify the prognosis of patients with MK$^+$ AML, especially regarding outcome after allogeneic HCT during first CR (CR1), we performed a retrospective analysis by using a dataset that included more than 2,000 AML patients in CR. Since failure to achieve CR is obviously associated with a dismal prognosis regardless of the presence or absence

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of MK, the present analysis focused on patients who achieved CR with one or two courses of chemotherapy.

Design and Methods

Patients

For this study, we used a Japanese nationwide database of adult AML patients. Eligible patients were required to be between 16 and 70 years of age, to be diagnosed with AML from 1999 to 2006 according to the World Health Organization (WHO) classification,[12] and to have achieved CR with one or two courses of chemotherapy. We excluded patients with acute promyelocytic leukemia (n=386) and those without pre-treatment cytogenetic results (n=36); this left 2,099 patients available for analysis. This study was approved by the Institutional Review Board at the National Cancer Center Hospital.

Cytogenetic analysis

Cytogenetic analysis was performed on metaphases from samples of bone marrow or blood obtained prior to induction therapy by using standard banding techniques. Karyotypes were determined according to the International System for Human Cytogenetic Nomenclature.[13] An abnormality was considered to be clonal when at least 2 metaphases had the same aberration in the case of either a structural abnormality or an additional chromosome. If there was a monosomy, it had to be present in at least 3 metaphases to be considered significant. Cytogenetics was classified as favorable, intermediate, unfavorable or unknown risk according to the Southwest Oncology Group (SWOG) criteria.[5] Apart from the SWOG classification, the MK status was assessed retrospectively for this study according to the definition proposed by Breems *et al.*[8] Accordingly, patients were divided into 4 cytogenetic subgroups: core binding factor AML (CBF AML), cytogenetically normal AML (CN AML), cytogenetically abnormal non-CBF AML without MK (MK^- AML), and cytogenetically abnormal non-CBF AML with MK (MK^+ AML).

Statistical analysis

A Kaplan-Meier survival analysis was performed to estimate the probabilities of OS and relapse-free survival (RFS). OS was defined as the time from the achievement of first CR (CR1) to death or last visit, and RFS as the time from the achievement of CR1 to relapse, death or last visit. Differences in OS and RFS between groups were compared by means of the log rank test. Cumulative incidences of relapse and non-relapse mortality were calculated with relapse considered as a competing risk for non-relapse mortality, and vice versa. Cox's regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were performed with the SPSS software version 11.0.1 (SPSS, Chicago, IL, USA) and R software version 2.13.0 (The R Foundation for Statistical Computing).

Results and Discussion

The entire cohort consisted of 2,099 AML patients who had achieved CR with one or two courses of chemotherapy, among whom CBF AML, CN AML, MK^- AML and MK^+ AML accounted for 21%, 49%, 27% and 4%, respectively. Table 1 shows the patients' characteristics according to these cytogenetic subgroups. Among the 73 patients with MK^+ AML, 68 (93%) had a cytogenetically unfavorable risk, while the remaining 5 had an unknown risk. In patients younger than 60 years, intensive therapy defined as "3+7" or its equivalent, was given to more than 95% in all of the cytogenetic subgroups. In patients aged 60 years or older, the proportion of those given intensive therapy seemed slightly lower in MK^+ AML but, nevertheless, 75% of them received intensive therapy.

Allogeneic HCT was performed in 32 patients with MK^+ AML, including 15 during CR1, 4 during second CR (CR2) and 13 during other disease phases. The details of patients who underwent allogeneic HCT in CR1 are summarized in the *Online Supplementary Table S1*. The median time from CR1 to transplantation was 93 days (range 14-540 days) for the 15 patients with MK^+ AML, which was significantly shorter than those in the other groups (P=0.011).

Figure 1A compares survival curves from the time of CR1 according to the cytogenetic subgroups. With a median follow up of 4.1 years for surviving patients, the 4-year probabilities of OS were 68% in CBF AML, 58% in CN AML, 46% in MK^- AML and 14% in MK^+ AML, respectively (P<0.001). This significantly inferior OS in MK^+ AML patients can mainly be explained by a high risk of relapse, since the relapse rate was 86% at four years, which was significantly higher than those in the remaining groups (P<0.001). No patient with MK^+ AML survived four years without allogeneic HCT, and the difference in OS was more pronounced when patients undergoing allogeneic HCT were analyzed as censored cases (83%, 66%, 54% and 0% at four years in CBF AML, CN AML, MK^- AML and MK^+ AML, respectively; P<0.001).

Next, we examined whether MK identified a very poor prognostic subset within 2 cytogenetically distinct subpopulations representing poor prognosis, i.e. unfavorable cyto-

Table 1. Patient's characteristics according to cytogenetic subgroup.

	CBF n=437	CN n=1,027	MK- n=562	MK+ n=73
Age, years				
Median	45	51	48	53
Range	16-70	16-70	16-70	20-70
Sex				
Male	279 (64%)	576 (56%)	311 (55%)	47 (64%)
Female	158 (36%)	451 (44%)	251 (45%)	26 (36%)
Cytogenetic risk by SWOG				
Favorable	411 (94%)	-	-	-
Intermediate	-	1,027 (100%)	64 (11%)	-
Unfavorable	26 (6%)	-	300 (53%)	68 (93%)
Unknown	-	-	198 (35%)	5 (7%)
WBC count, $\times 10^9$/L				
Median	11.2	13.0	8.5	4.4
Range	0.7-281.2	0.4-40.2	0.3-22.3	0.8-408.0
Dysplasia				
Yes	35 (8%)	220 (20%)	136 (24%)	33 (45%)
No	402 (92%)	807 (80%)	426 (76%)	40 (55%)
N. induction courses				
1 course	378 (86%)	825 (80%)	419 (75%)	56 (77%)
2 courses	59 (14%)	202 (20%)	143 (25%)	17 (23%)
Allogeneic HCT				
CR1	32 (7%)	256 (25%)	183 (33%)	15 (21%)
CR2	78 (18%)	106 (10%)	57 (10%)	4 (5%)
Other disease phase	66 (15%)	125 (12%)	87 (15%)	13 (18%)
Not performed	261 (60%)	540 (53%)	235 (42%)	41 (56%)

CBF: core binding factor AML; CN: cytogenetically normal AML; MK-: cytogenetically abnormal non-CBF AML without monosomal karyotype; MK+: cytogenetically abnormal non-CBF AML with monosomal karyotype; SWOG: Southwest Oncology Group; WBC: white blood cell count; HCT: hematopoietic cell transplantation; CR1: first complete remission; CR2: second complete remission.

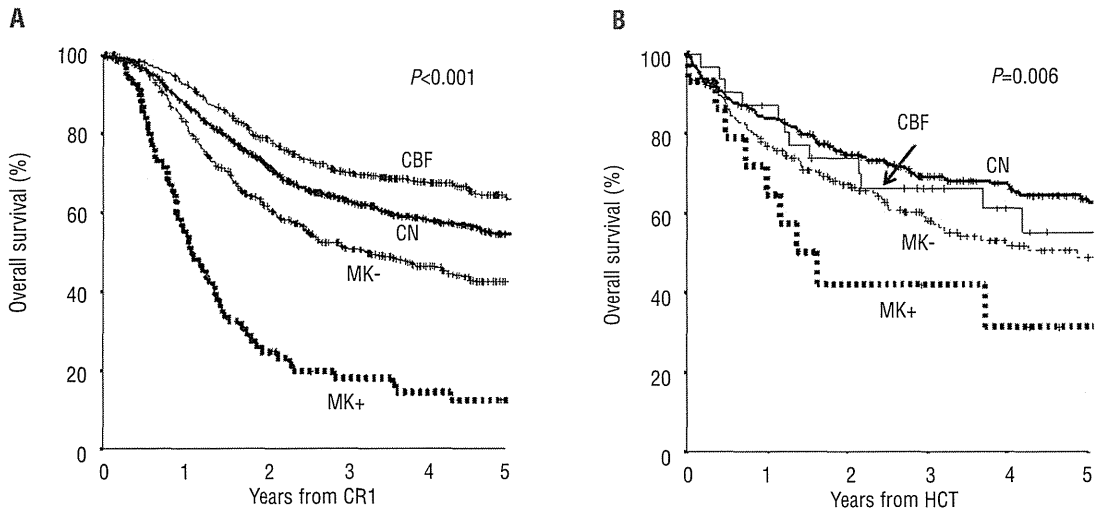

Figure 1. Kaplan-Meier curves for (A) OS after achieving CR1 for the entire cohort, and for (B) OS after allogeneic HCT for patients who underwent allogeneic HCT in CR1, according to the cytogenetic subgroups. CBF represents core binding factor AML; CN: cytogenetically normal AML; MK$^-$, cytogenetically abnormal non-CBF AML without monosomal karyotype; MK$^+$, cytogenetically abnormal non-CBF AML with monosomal karyotype. *P* values are presented for comparisons among the 4 groups.

genetics and CK. MK accounted for 17% of those with unfavorable cytogenetics (68 of 394), and 41% of those with CK (39 of 96). Among patients with unfavorable cytogenetics, there was a statistically significant difference in OS between those with and without MK (16% *vs.* 46% at four years, *P*<0.001; *Online Supplementary Figure S1A*). Similar findings were seen in patients with CK, with 4-year OS rates of 11% and 34% in those with and without MK (*P*<0.001; *Online Supplementary Figure S1B*).

Allogeneic HCT was performed during CR1 in 32 of 437 CBF AML patients (7%), 256 of 1,027 CN AML patients (25%), 183 of 562 MK$^-$ AML patients (33%), and 15 of 73 MK$^+$ AML patients (21%). Figure 1B shows Kaplan-Meier curves for OS after HCT in patients who were transplanted during CR1. These subgroups showed significantly different OS, with 4-year OS rates of 61%, 67%, 52% and 31% in CBF AML, CN AML, MK$^-$ AML, and MK$^+$ AML, respectively (*P*=0.006). A statistically significant difference was observed in terms of post-transplant relapse (*P*=0.025) (*Online Supplementary Table S2*). Non-relapse mortality in patients with MK$^+$ AML appeared to be higher than those in the other groups, but these differences were not statistically significant (*P*=0.595). Table 2 shows results of univariate and multivariate analyses on factors associated with post-transplant OS in patients undergoing allogeneic HCT in CR1. After adjusting for other covariates, MK remained significantly associated with inferior post-transplant OS (HR 3.12; 95% CI, 1.58-6.15; *P*=0.001, with reference to CN AML).

MK is a recently proposed subgroup of cytogenetic abnormalities that confers a very unfavorable prognosis in AML.[8] Reported CR rates have been quite low, ranging between 18 and 48%,[8-10] and this represents a major cause of the poor prognosis. Since patients who fail to achieve CR generally have a very unfavorable prognosis regardless of the presence or absence of MK, we decided to restrict our analysis to patients who had achieved CR. In our patient population, MK was observed in 4%; this was lower than the values reported previously (6-13%).[7-9] The most probable explanation for this could be the fact that our cohort included only patients who had achieved CR, while the other studies included newly diagnosed patients.

Our data clearly demonstrated that MK confers a significantly worse prognosis in patients who have achieved CR. Notably, MK identified patients with a worse prognosis

Table 2. Factors associated with post-transplant OS in patients who underwent allogeneic HCT in CR1.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Cytogenetic subgroup				
CBF	1.14 (0.62-2.09)	0.671	1.17 (0.63-2.15)	0.622
CN	1.00	-	1.00	-
MK$^-$	1.43 (1.05-1.96)	0.023	1.45 (1.06-1.98)	0.021
MK$^+$	2.74 (1.42-5.28)	0.003	3.12 (1.58-6.15)	0.001
Age				
As a numerical variable (1 year older)	1.01 (1.00-1.02)	0.294	1.01 (0.99-1.02)	0.377
Sex				
Male	1.00	-	1.00	-
Female	1.08 (0.81-1.45)	0.597	1.16 (0.86-1.57)	0.327
WBC count				
As a numerical variable (10×10^9/L lower)	1.02 (1.00-1.03)	0.037	1.02 (1.01-1.04)	0.007
Donor				
Related*	1.00	-	1.00	-
Other	1.39 (1.04-1.87)	0.026	1.47 (1.09-1.98)	0.011
Conditioning				
Myeloablative	1.00	-	1.00	-
Reduced-intensity	1.13 (0.81-1.58)	0.465	1.04 (0.70-1.56)	0.846

*HR: hazard ratio; CI: confidence interval; CBF: core binding factor AML; CN: cytogenetically normal AML; MK$^-$: cytogenetically abnormal non-CBF AML without monosomal karyotype; MK$^+$: cytogenetically abnormal non-CBF AML with monosomal karyotype; WBC: white blood cell count. *"Related" indicates a matched or 1 antigen-mismatched family donor.*

even among those with unfavorable cytogenetics or those with CK. The detrimental prognostic impact of MK was primarily due to high relapse rates and, importantly, similar results were seen in patients who received allogeneic HCT in CR1. Post-transplant relapse occurred more than 20% more frequently in MK+ AML patients than in those in each of the remaining cytogenetic subgroups. This finding is consistent with published studies.[11,14] Investigators at the University of Minnesota analyzed 134 AML patients, including 17 patients with MK who were allografted in CR1, and showed that the MK classification could significantly predict the risk of post-transplant relapse.[14] A report from the Fred Hutchinson Cancer Research Center described the outcome of 35 patients with MK and 193 patients without MK who underwent allogeneic HCT in CR1, in which the 4-year OS rates were 30 and 65% in those with and without MK.[11] Those results taken together with our present results suggest that allogeneic HCT may be able to improve but not completely override the poor prognosis with MK+ AML. It is widely recognized that allogeneic HCT in CR1 is the treatment of choice for patients with AML at cytogenetically unfavorable risk,[15-17] if they have a suitable donor and are fit enough to undergo the procedure. In this study, allogeneic HCT was given to only 21% of patients with MK+ AML during CR1. This low transplantation rate could partly be due to a short CR1 duration, which likely decreased the chance of receiving allogeneic HCT in CR1. A significantly shorter time to transplantation in our MK+ AML patients might reflect the short duration of their CR1 that precluded an implementation of allogeneic HCT after a relatively long interval after achieving CR. Despite a considerable risk of relapse even after transplantation, it is still conceivable that these cytogenetically very unfavorable patients would benefit from allogeneic HCT. We observed that no patient survived long-term without allogeneic HCT, which is in line with reports from the SWOG study.[9]

Our study has several limitations and the results must, therefore, be interpreted with caution. These limitations include the retrospective nature of the study, and the relatively small number of patients with MK+ AML, especially of those who underwent allogeneic HCT in CR1, leaving room for selection bias or chance effect. However, given that MK+ AML accounted for only 4% of our AML patients in CR, it would be quite impractical to conduct a prospective comparison to assess the role of allogeneic HCT in CR1. Under such conditions, the findings from a large-scale retrospective study could have important implications.

In summary, our data confirm that MK exerts a significantly adverse effect on post-remission outcome in AML patients treated with and without allogeneic HCT in CR1. Although our results suggest that allogeneic HCT is already an available treatment of choice, the development of alternative therapies is warranted for this patient population.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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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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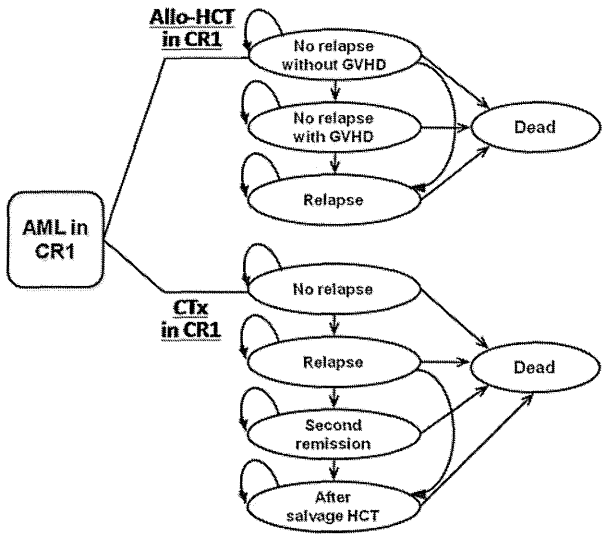

Figure 1. Markov decision model. Markov model that compares allo-HCT in CR1 and chemotherapy in CR1 is shown. Possible health states for each of the 2 groups are indicated in circles. Arrows indicate possible transitions between states. CR1 indicates first complete remission; allo-HCT, allogeneic hematopoietic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

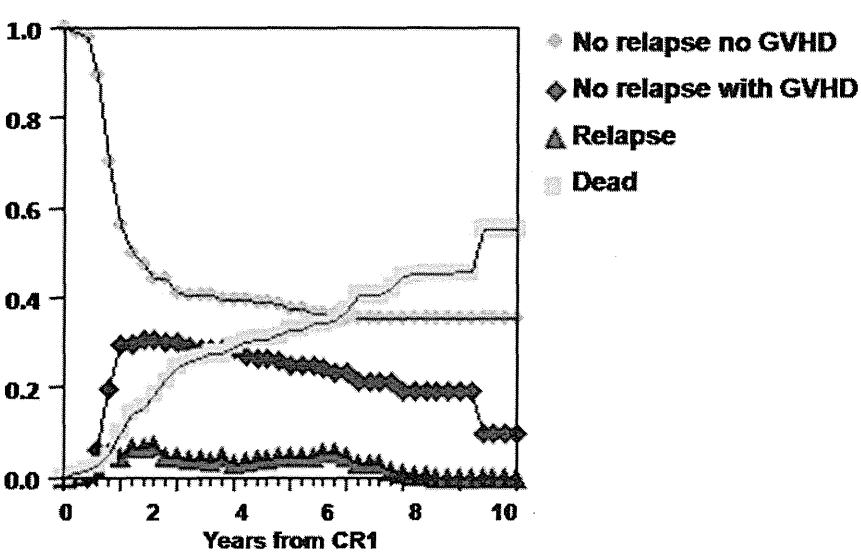

Figure 2. Distribution of patients in each health state. Distribution of patients with intermediate-risk AML in each health state is shown. Transition probabilities between the states were calculated for each subgroup with the use of the database. The probabilities of state transition were allowed to 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."

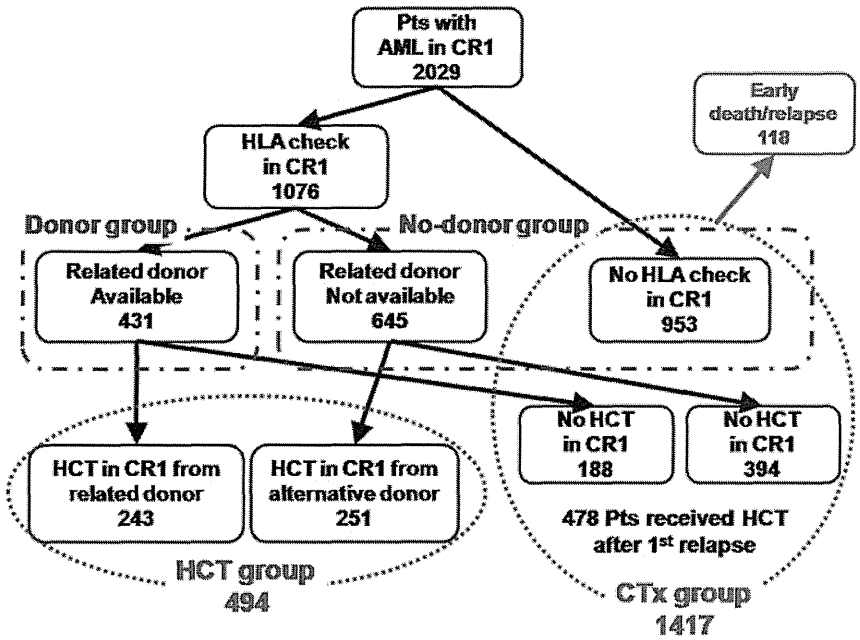

Figure 3. Patient flow. The flow of HLA check, donor availability, and actual application of allo-HCT in CR1 are shown. Among the total of 2029 patients with AML in CR1, 494 received allo-HCT in CR1 and were included in the HCT group. Among the remaining 1535 patients, 118 patients who died or relapsed 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

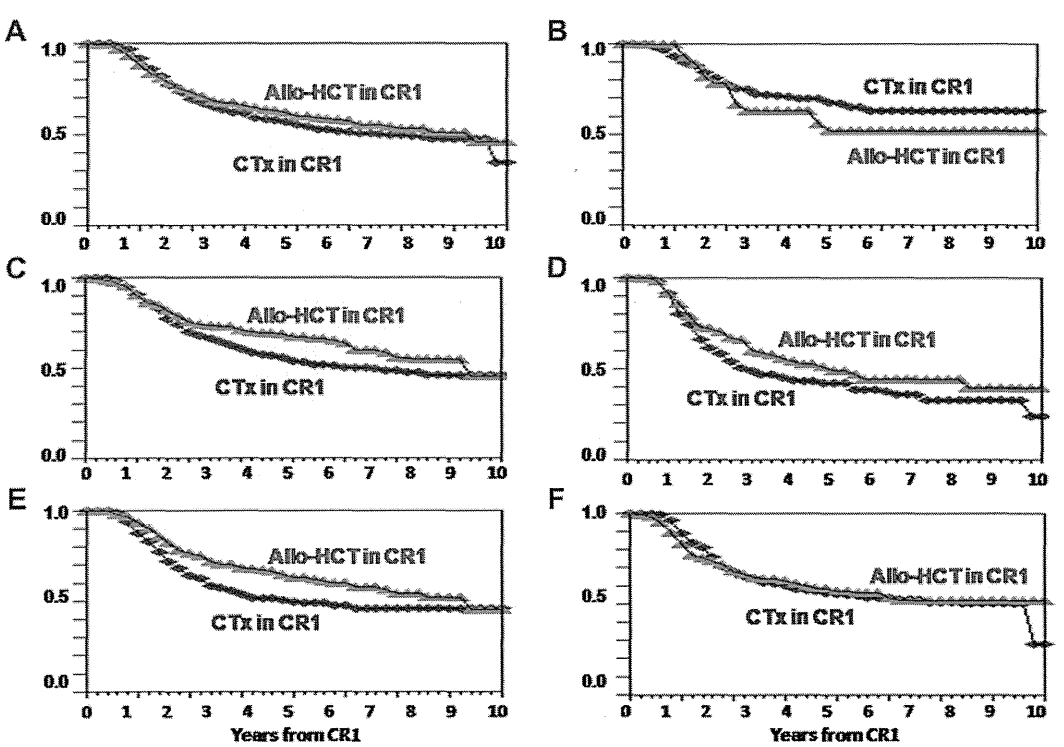

Figure 4. Survival curves of allo-HCT versus CTx by TreeAge. The overall survival curves of the HCT and CTx groups depicted by TreeAge Pro 2009 in (A) total patients, (B) SWOG favorable-risk group, (C) intermediate-risk group, (D) unfavorable-risk group, (E) donor group, and (F) no-donor group. allo-HCT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

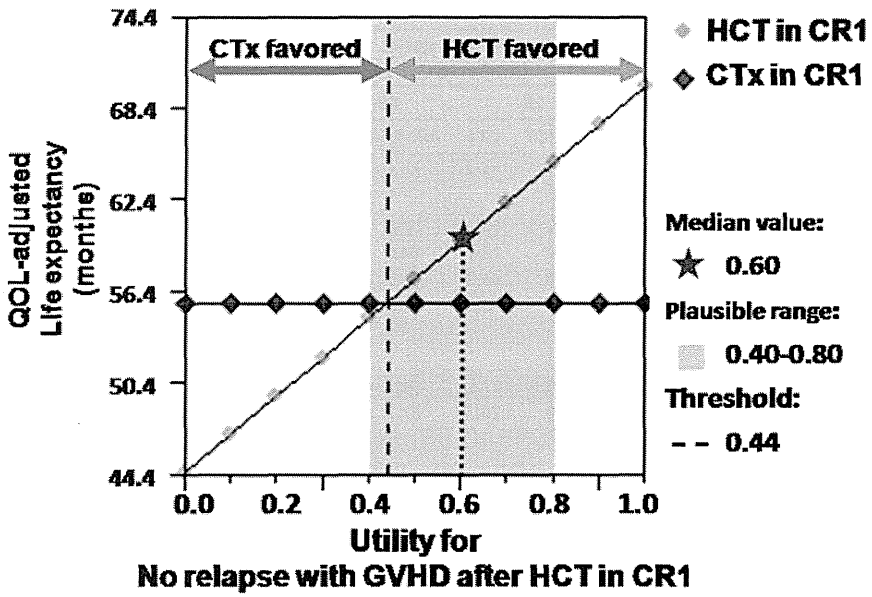

Figure 5. One-way sensitivity analysis. One-way sensitivity analysis for the utility of the state "No relapse with GVHD" after allogeneic transplantation in CR1 among patients with intermediate-risk AML is shown. The green dot represents the QOL-adjusted life expectancy when allo-HCT was performed in 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

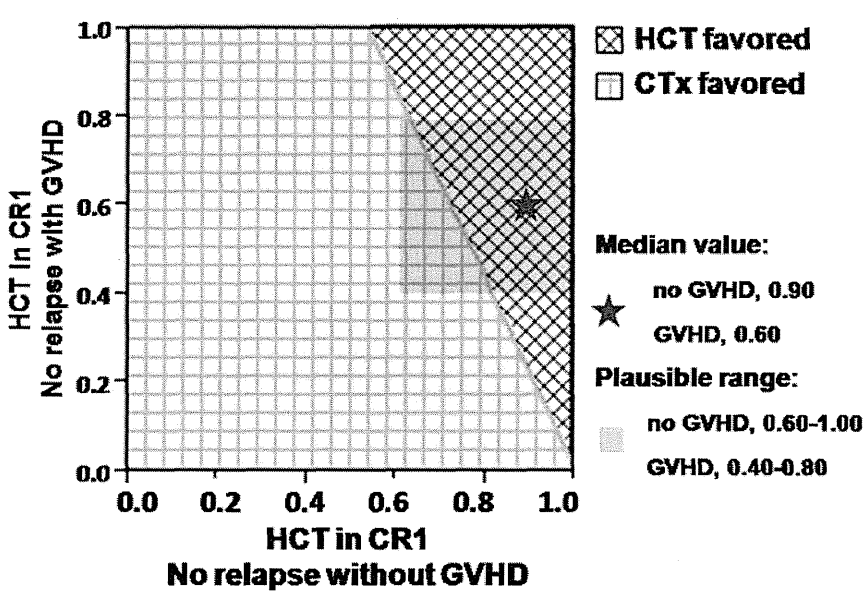

Figure 6. Two-way sensitivity analysis. Two-way sensitivity analysis for the utilities of the states "No relapse without GVHD" and "No relapse with GVHD." The blue area represents the range in which HCT is favored. The green area represents the range in which CTx is favored. Although the median value (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.