Scandinavian Journal of Infectious Diseases, 2012; 44: 60–64

informa
healthcare

SHORT COMMUNICATION

Correlation between serum linezolid concentration and the development of thrombocytopenia

YOICHI HIRAKI[1], YASUHIRO TSUJI[2], MIKAKO HIRAIKE[1], NOBUHIRO MISUMI[1], KANA MATSUMOTO[3], KUNIHIKO MORITA[3], HIDETOSHI KAMIMURA[4] & YOSHIHARU KARUBE[4]

From the [1]Department of Pharmacy, National Hospital Organization Kumamoto Medical Center, Kumamoto, Kumamoto, [2]Department of Pharmacy, Sasebo Chuo Hospital, Sasebo, Nagasaki, [3]Department of Clinical Pharmaceutics, Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe, Kyoto, and [4]Faculty of Pharmaceutical Sciences, Fukuoka University, Johnan-ku, Fukuoka, Japan

Abstract
We evaluated the possible association between trough linezolid (LZD) concentrations and platelet counts using a dose–response curve with a logit model equation. We demonstrated that trough LZD concentrations correlated with platelet counts. A significant decrease in platelet count was observed in patients with trough LZD concentrations higher than 22.1 μg/ml.

Keywords: *Dose–response curve, linezolid, logit analysis, renal dysfunction, thrombocytopenia*

Introduction

Linezolid (LZD) is a novel synthetic oxazolidinone antimicrobial agent with a unique mechanism of action compared with other existing agents [1]. Notably, LZD has proven effective for the treatment of infections caused by multidrug-resistant Gram-positive cocci, including vancomycin-resistant Staphylococcus aureus (VRSA), vancomycin-resistant Enterococcus (VRE), and penicillin-resistant Streptococcus pneumoniae (PRSP), for which many current antimicrobial therapies are inadequate [2–4]. Although LZD treatment has been associated with similar or higher clinical response rates than vancomycin for methicillin-resistant S. aureus pneumonia [5], its use is not without risk. A high incidence of reversible thrombocytopenia has been reported in LZD-treated patients, particularly in those treated for 2 weeks or more [6–8]. Notably, Wu et al. [6] performed a survival analysis for development of thrombocytopenia or death and detected significant differences ($p < 0.001$) between patients with end-stage and non-end-stage renal disease. Our group also detected high trough concentrations of LZD in patients with renal dysfunction, leading us to speculate that these patients have delayed elimination of LZD, which may be a factor in the development of thrombocytopenia [9]. However, no association between trough LZD concentrations and the rate of decrease in platelet (PLT) counts has been reported to date.

The present prospective study was conducted to investigate the relationship between trough LZD concentrations and PLT counts using logit model analysis and a bootstrapping method. In addition, we assessed the effect of renal dysfunction on trough LZD concentration and PLT counts.

Methods

Patients

All subjects provided informed consent to participate in this study prior to the first administration of LZD

Correspondence: Y. Hiraki, Department of Pharmacy, National Hospital Organization Kumamoto Medical Center, 1-5 Ninomaru, Kumamoto, Kumamoto 860-0008, Japan. Tel: +81 96 353 6501. Fax: +81 96 325 2519. E-mail: hiraki@kumamoto2.hosp.go.jp

(Received 23 January 2011; accepted 21 July 2011)

ISSN 0036-5548 print/ISSN 1651-1980 online
DOI: 10.3109/00365548.2011.608712

for the treatment of pneumonia. Patients with disseminated intravascular coagulation (DIC) and multiple organ failure (MOF), undergoing dialysis, or with a disease that might affect PLT counts, such as sepsis, were excluded from this study. In addition, patients who received a blood transfusion or drugs that could affect PLT counts, before or during LZD administration, were also excluded from this study.

Medications warranting exclusion

Patients who underwent treatment with the following agents were excluded from the present study: heparin, enoxaparin, valproic acid, gold drug, penicillin, cephalosporin antibiotics, sulfonamides, alpha-interferon, digoxin, digitoxin, procaine amide, cimetidine, and ranitidine.

LZD treatment and blood collection

Patients received LZD 600 mg by intravenous infusion over 60 to 120 min every 12 h. Blood was collected immediately before LZD administration for measurement of serum LZD concentration on or after the 4th day following drug initiation (at which time the LZD level was assumed to have reached a steady state) and subsequently on arbitrary days during the treatment period. The same blood samples were used to determine serum LZD and creatinine (SCr) concentrations and PLT counts.

Measurement of serum LZD concentrations

The serum LZD levels were measured by high-performance liquid chromatography (HPLC), as previously described [10]. Briefly, blood samples were first deproteinized using an equivalent volume of acetonitrile and then centrifuged at 5000 rpm for 10 min at 4°C. The resulting supernatant was subjected to HPLC, employing the absolute calibration method. For the measurement, 20-µl samples were loaded onto an octadecyl silane (ODS) Hypersil column (4.6 mm ID × 150 mm; Thermo Scientific Co., Yokohama, Japan). The HPLC system (CBM-20A, Shimadzu Co., Kyoto, Japan) consisted of an LC-20AT flow pump and SPD-10AV VP ultraviolet (UV) detector (Shimadzu Co.). As the mobile phase, a solution of 1% orthophosphoric acid, 30% methanol, and 2 g/l heptane sulfonic acid (adjusted to pH 5 with 10 M sodium hydroxide) was used at a flow rate of 1.0 ml/min. LZD in the samples was measured at a wavelength of 254 nm, and the lower limit of detection in this analysis was 0.1 µg/ml.

Determination of SCr levels and creatinine clearance rate

The creatinine clearance rate (CLCr) for each of the patients included in the study was estimated from the SCr concentration using the Cockcroft–Gault equation [11]. Patients with a CLCr of less than 60 ml/min were judged to have renal dysfunction.

Measurement of serum PLT counts

The PLT count measured before the first administration of LZD was determined to be the PLT baseline. The PLT count that displayed the greatest degree of deterioration from the baseline during the administration of LZD was considered the PLT minimum value. The rate of decrease in PLT counts (Y) was calculated using the following equation: $Y = 1 - (B/A)$, where A is the PLT baseline, and B is the PLT minimum value.

Dose–response curve determination using the logit model

We evaluated the association between LZD concentration and the decrease in PLT counts through dose–response curve determination using the logit model, in which the independent and dependent variables were the natural logarithm (ln) of the LZD concentration (x) and the decrease in PLT (y), respectively. The data analysis was performed using R software and the generalized linear model (GLM) function (family = binomial) [12]. To estimate the 95% confidence intervals (CI), and α and β values used in the non-parametric bootstrapping method [13], we utilized the following logit model equation:

$$p = \frac{1}{1 + exp\,(-a - \beta x)}$$

where p is the probability of a binary outcome, x is a continuous stimulus or exposure variable (trough LZD concentration), α determines the location of the curve on the x-axis, and β represents the slope of the curve.

Extrapolation was performed based on the dependent variable (PLT decrease). For all values greater than 0.7, the rate of decrease in PLT counts was considered to be 1.0. We also calculated the 50% hazard ratio of the dose–response curve using the equation: exp (α/β).

Statistical analysis

Statistical differences were assessed using the Mann–Whitney U-test with the significance level

set at $p < 0.05$. Statistical analysis was performed using SPSS analysis software v. 18 (SPSS, Inc., Tokyo, Japan).

Ethics

This study was approved by the ethics committee of the National Hospital Organization Kumamoto Medical Center, and was conducted in accordance with the ethics guidelines of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study was explained to the patients in writing, and written informed consent was obtained from each study participant.

Results

Eight patients with pneumonia (3 males and 5 females) participated in the study. Five of the patients had normal renal function and a mean ± standard deviation (SD) age of 65.2 ± 15.1 y, body weight of 49.0 ± 9.4 kg, SCr of 0.56 ± 0.2 mg/dl, CLCr of 94.5 ± 49.8 ml/min, and LZD therapy duration of 14.4 ± 15.5 days. The other 3 patients had renal dysfunction and a mean ± SD age of 63.7 ± 4.7 y, body weight of 64.7 ± 6.8 kg, SCr of 3.4 ± 2.2 mg/dl, CLCr of 28.9 ± 27.1 ml/min, and LZD therapy duration of 14 ± 1.7 days. No significant differences were detected in the duration of therapy between patients who had normal renal function and those who exhibited renal dysfunction (Table I). The individual patient characteristics, including therapy duration, trough LZD concentrations, and PLT counts, are summarized in Table I.

We determined the mean trough LZD concentrations and compared the baseline PLT counts and the PLT minimum value during LZD administration. In total, 21 samples were collected from the 8 patients. The mean trough LZD concentration of all 8 patients was 30.4 ± 21.4 μg/ml (range 7.5–90.9 μg/ml), but was significantly different between the patients with and without renal dysfunction, with mean values of 43.5 ± 25.5 and 19.7 ± 8.2 μg/ml, respectively ($p = 0.0402$). A decrease in the PLT count of greater than 50% was observed for 5 of 8 patients, which included the 3 patients with impaired renal function. The mean PLT counts of the patients without renal dysfunction before and after administration were 197.2 ± 53.7 × 10^3/μl and 189.2 ± 130.4 × 10^3/μl, respectively ($p = 0.68$), compared with 274.3 ± 70.0 × 10^3/μl and 69.7 ± 29.3. × 10^3/μl, respectively ($p = 0.05$), in the patients with renal dysfunction.

Finally, to examine the association between LZD trough concentrations and PLT counts, the values determined for all 8 patients were examined by logit model analysis. In addition, the 95% CIs were estimated using a bootstrapping method. A dose–response curve was obtained by convergence of the logit model, in which the estimated α and β values were −12.7 (97.5% CI − 11.60–14.10, $p < 0.0001$) and 4.1 (97.5% CI 4.54–3.75, $p < 0.0001$), respectively, while Akaike's information criterion (AIC) was 250.4 (Figure 1). Our analysis revealed that the trough LZD concentrations and PLT counts for each patient fit the dose–response curve. From the logit regression analysis, we determined that the 50% hazard ratio for the development of thrombocytopenia correlated to a trough LZD concentration of 22.1 μg/ml.

Discussion

In this study, we hypothesized that high trough LZD concentrations, which develop as a result of delayed elimination of LZD, particularly in patients with

Table I. Characteristics, linezolid trough concentrations, and platelet counts of the 8 patients with infective pneumonia treated with linezolid.

	Patient	Age (y)	Weight (kg)	CLCr (ml/min)	Therapy duration (days)	Mean LZD trough concentration[a] (μg/ml)	Day 0[b] PLT count (×10^3/μl)	Minimum PLT count (×10^3/μl)	Day of minimum PLT count
Normal renal function	1	46	39.8	64.3	8	31.7 ± 12.9	272	377	7
	2	58	60.0	179.5	9	7.5 ± 0.7	190	255	7
	3	61	52.0	99.0	7	16.5 ± 1.0	169	169	6
	4	80	54.4	62.9	6	22.8 ± 1.2	224	92	6
	5	81	38.6	66.8	42	18.3 ± 2.5	131	53	12
Renal dysfunction	6	60	67.4	59.8	16	65.2 ± 18.6	204	65	8
	7	62	69.7	17.9	13	20.5 ± 6.6	275	43	7
	8	69	56.9	9.0	13	48.8 ± 2.3	344	101	8

CLCr, creatinine clearance rate; LZD, linezolid. PLT, platelet.
[a]Mean LZD trough concentrations are shown as the mean ± standard deviation.
[b]Day 0 = before the first administration of LZD.

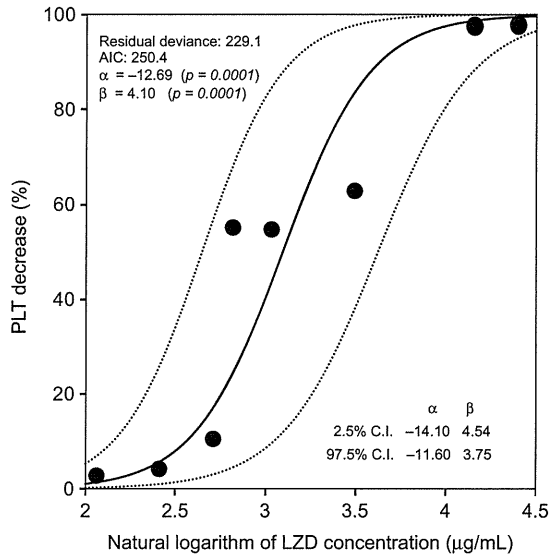

Figure 1. Logit analysis for the natural logarithm of the trough linezolid (LZD) concentration (μg/ml) and the rate of decrease in platelet (PLT) count (%) from baseline (before the first LZD administration) levels. The model adaptability was evaluated by the bootstrapping method ($n = 1000$). The continuous line depicts the predicted logit (p) and the dotted lines 95% confidence interval (95% CI). AIC, Akaike's information criterion; α, location of the curve on the x-axis; β, slope of the curve; •, measured value.

renal dysfunction, can lead to thrombocytopenia. By analyzing the association between trough LZD concentrations (independent variable, x) and PLT counts (dependent variable, y) using the logit model [13], we determined that the 50% hazard ratio for the development of thrombocytopenia correlated to a trough LZD concentration of 22.1 μg/ml. The PLT count also decreased as the trough LZD concentration increased in patients with normal renal function. As the 3 patients with renal dysfunction had LZD levels that exceeded 22.1 μg/ml, our preliminary results suggest that thrombocytopenia may develop with increased trough LZD concentrations in patients with delayed LZD elimination, and thrombocytopenia necessitates LZD treatment discontinuation.

The elevation in serum LZD concentration appeared to correlate with the PLT count, as all 3 patients with renal dysfunction exhibited decreases in PLT counts greater than 50% following LZD treatment, whereas only 2 patients with normal renal function had a marked reduction of PLT counts. Notably, however, the reduction in the latter 2 patients was not as severe as that observed in the patients with renal dysfunction, and 1 of the patients with normal renal function had received LZD treatment approximately 1 month longer than all other patients.

In general, dose adjustment of LZD is considered unnecessary, even for patients with mild to moderate renal or hepatic disorders, as LZD is predominantly metabolized through oxidation of its morpholine ring to an inactive form by non-enzymatic oxidative reactions [4]. However, in patients with renal dysfunction, Lin et al. [14] reported that thrombocytopenia often develops when the duration of LZD administration is longer than 14 days. Furthermore, Tsuji et al. [9] and Matsumoto et al. [15] suggested that the rise in the LZD concentration and in the area under the plasma LZD concentration–time curve over 24 h (AUC24h) are factors in the development of thrombocytopenia in patients with renal dysfunction. Our study provides additional support for the association between elevated LZD trough concentrations and decreases in PLT counts in patients with renal dysfunction.

Several limitations of the study warrant mention. First, due to the limited number of patients given LZD at our institution without exclusion criteria, only 8 patients were included in this study, thus limiting the significance of the findings. Second, blood collection was not performed to a defined schedule because the blood samples used in the study were those collected during the routine care of the patients. Finally, we only investigated the relationship between PLT counts and LZD concentration in this study. Data on confounding factors that can decrease PLT counts, such as co-morbidities and severity of illness, were not collected; thus, we cannot eliminate the possibility that PLT counts were influenced by factors aside from LZD concentrations.

In conclusion, we found that elevated LZD trough concentrations in patients with renal dysfunction were associated with low PLT counts. Although these findings are preliminary, our logit regression analysis suggests that a trough LZD concentration that exceeds 22 μg/ml may lead to the development of thrombocytopenia. Therefore, PLT levels should be monitored more closely to prevent thrombocytopenia in patients with renal dysfunction receiving LZD. Further investigations of this association are warranted, including whether reductions in the LZD dose will decrease the risk of thrombocytopenia in patients with renal dysfunction.

Declaration of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Zurenko GE, Gibson JK, Shinabarger DL, Aristoff PA, Ford CW, Tarpley WG. Oxazolidinones: a new class of antibacterials. Curr Opin Pharmacol 2001;1:470–6.

[2] Mascini EM, Troelstra A, Beitsma M, Blok HE, Jalink KP, Hopmans TE, et al. Genotyping and preemptive isolation to control an outbreak of vancomycin-resistant Enterococcus faecium. Clin Infect Dis 2006;42:739–46.
[3] Chang S, Sievert DM, Hageman JC, Boulton ML, Tenover FC, Downes FP, et al. Infection with vancomycin-resistant Staphylococcus aureus containing the *vanA* resistance gene. N Engl J Med 2003;348:1342–7.
[4] Pfizer. ZYVOX (linezolid) label information. Pfizer; 2008. Retrieved 20 June 2008.
[5] Pfizer Co. New phase 4 study shows higher rates of clinical and microbiological success for Zyvox versus vancomycin in MRSA nosocomial pneumonia. The 48th Annual Meeting of the Infectious Diseases Society of America, Vancouver, Canada, October 21–24, 2010.
[6] Wu VC, Wang YT, Wang CY, Tsai IJ, Wu KD, Hwang JJ, et al. High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. Clin Infect Dis 2006;42:66–72.
[7] Minson Q, Gentry CA. Analysis of linezolid-associated hematologic toxicities in a large veterans affairs medical center. Pharmacotherapy 2010;30:895–903.
[8] Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, et al. Hematologic effects of linezolid: summary of clinical experience. Antimicrob Agents Chemother 2002;46: 2723–6.
[9] Tsuji Y, Hiraki Y, Matsumoto K, Mizoguchi A, Kobayashi T, Sadoh S, et al. Thrombocytopenia and anemia caused by a persistent high linezolid concentration in patients with renal dysfunction. J Infect Chemother 2010;17: 70–5.
[10] Majcher-Peszynska J, Haase G, Sass M, Mundkowski R, Pietsch A, Klammt S, et al. Pharmacokinetics and penetration of linezolid into inflamed soft tissue in diabetic foot infections. Eur J Clin Pharmacol 2008;64:1093–100.
[11] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[12] Ihaka R, Gentleman R. R: A language for data analysis and graphics. J Comput Graph Stat 1996;5:299–314.
[13] Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. Stat Med 1992;11:2093–109.
[14] Lin YH, Wu VC, Tsai IJ, Ho YL, Hwang JJ, Tsau YK, et al. High frequency of linezolid-associated thrombocytopenia among patients with renal insufficiency. Int J Antimicrob Agents 2006;28:345–51.
[15] Matsumoto K, Takeshita A, Ikawa K, Shigemi A, Yaji K, Shimodozono Y, et al. Higher linezolid exposure and higher frequency of thrombocytopenia in patients with renal dysfunction. Int J Antimicrob Agents 2010;36: 179–81.

Clinical and Experimental Hypertension, 33(3): 147–152, (2011)

ISSN 1064-1963 print/1525-6006 online
DOI: 10.3109/10641963.2010.531839

informa
healthcare

Individual Assessment of Inherent Arterial Stiffness Using Nomogram and Pulse Wave Velocity Index: The Ohasama Study

Rieko Hatanaka,[1,2] Taku Obara,[1,3] Daisuke Watabe,[1] Atsushi Kimura,[1] Tomohiro Hanazawa,[1] Hiromi Ohba,[1] Tomofumi Ishikawa,[1] Tomoyuki Aikawa,[4] Azusa Hara,[1] Hirohito Metoki,[1,5] Kei Asayama,[4] Masahiro Kikuya,[1] Takayoshi Ohkubo,[1,4] Kazuhito Totsune,[1] Yutaka Imai[1,4]

[1]Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, [2]Department of Functional Brain Imaging, Institute of Development, Aging and Cancer (IDAC), Tohoku University, [3]Department of Pharmacy, Tohoku University Hospital, [4]Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences, [5]Department of Medical Genetics, Tohoku University Graduated School of Medicine, Sendai, Japan

Abstract

We measured the brachial-ankle pulse wave velocity (baPWV) in 491 normotensives and determined the "PWV index" (measured baPWV–theoretical baPWV) in 491 normotensives and 83 controlled hypertensives. Linear regression analysis revealed that the theoretical baPWV (cm/sec) was 0.21 × age^2 (years^2)−13.73 × age (years) + 0.05 × mean arterial pressure^2 (mmHg^2) + 3.95 × heart rate (bpm) + 36.49 × gender (1 male; 0 female) + 733 (R^2 = 0.53). The calculated PWV index was significantly higher in 13 smokers than 70 nonsmokers among controlled hypertensives. The calculated PWV index might provide more precise information about inherent arterial stiffness.

Keywords: arterial stiffness, pulse wave velocity, nomogram

INTRODUCTION

The elastic properties of the large arteries are important determinants of circulatory physiology in health and disease. Arterial stiffness plays an important role in the pathogenesis of cerebrovascular and cardiovascular disease (1–3). Arterial stiffening increases ventricular afterload through earlier return of the reflected wave (4), and reduces coronary blood flow by decreasing diastolic pressure (5). This leads to cardiovascular events, such as coronary ischemia and heart failure (5, 6). Arterial stiffness is also associated with microvascular diseases (7). Therefore, evaluation of inherent arterial stiffness for individuals could help not only risk assessment but also risk reduction through effective treatment.

Measuring pulse wave velocity (PWV) is one of the most representative methods for assessing arterial stiffness (8, 9). However, normative values of PWV have not yet been fully defined. A single, specific PWV value as a cut-off is inappropriate because various physiological factors, such as age (10, 11), blood pressure (BP) (11, 12), heart rate (HR) (13, 14), and gender (15) affect PWV. Therefore, to evaluate "inherent" arterial stiffness in individuals, the confounding effect of these factors must be considered. Although Blacher et al. (16) have calculated a PWV index that could reflect inherent arterial stiffness in patients with end-stage renal disease, this has not been achieved in an apparently healthy general population. Over the past several years, in addition to conventional carotid-femoral PWV (cfPWV) measurements, the brachial-ankle PWV (baPWV) can provide useful information about arterial stiffness (17, 18), particularly in large populations (19). Therefore, we aimed to construct a nomogram for theoretical baPWV in a general population and to propose an index of inherent arterial stiffness which might be better related to cardiovascular risk for individuals.

METHODS

Study Subjects

The present study was based on a health examination survey performed on residents of Ohasama town, Japan, who were aged 34 years or older. The geographic and demographic characteristics of Ohasama have been reported elsewhere (20). Of 1612 individuals

Address correspondence to Rieko Hatanaka, Department of Functional Brain Imaging, Institute of Development, Aging and Cancer (IDAC), Tohoku University, 4-1, Seiryo-cho, Aoba-ku, Sendai 980-8575, Japan. E-mail: rieko@idac.tohoku.ac.jp

Received 2 March 2010; revised 16 April 2010; accepted 29 April 2010.

who underwent a health examination, we selected 491 healthy subjects, according to the following criteria: normotension (systolic BP [SBP] <140 mmHg, diastolic BP [DBP] <90 mmHg, and no medication for hypertension), nondiabetes (fasting blood glucose <126 mg/dl or post-prandial glucose <200 mg/dl, and no medication with insulin or oral hypoglycemic agents), normocholesteloremia (total cholesterol <240 mg/dl and no medication for dyslipidemia), ankle-brachial index (ABI) >0.9, no history of cardiovascular and cerebrovascular diseases, and body mass index (BMI) <30 kg/m^2. These individuals were defined as healthy and normotensive and we constructed a nomogram for calculating theoretical PWV using data from these participants.

We also selected another group of 83 hypertensive patients whose BP was controlled with anti-hypertensive medication. The selection criteria for the hypertensive patients are the same as the one mentioned except treatment by medications for hypertension. They were defined as having controlled hypertension.

Biochemical data were obtained from venous blood samples collected on the same days as the PWV measurements. Information concerning lifestyle, habits, and therapeutic status was collected using a questionnaire.

The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine, the Department of Health of the Ohasama Town Government, and conducted in accordance with the Declaration of Helsinki and its amendments. All participants gave informed, written consent.

Measurement of PWV

The baPWV was measured in the supine position after at least 5 min of rest using an automatic device (Form PWV/ABI; Colin Co., Ltd., Komaki, Japan), as described (17, 19). Thus, cuffs connected to a plethysmographic sensor are wrapped on both the brachia and ankles for pressure waveforms recordings. The baPWV was determined as length of an arterial segment by the transit time of the pulse wave: baPWV = (La-Lb)/T, where T is the time difference in the foot between the right brachial pulse wave and the right ankle pulse wave, La is the path length from the suprasternal notch to the ankle, and Lb is the path length from the suprasternal notch to the brachium. La and Lb are automatically calculated according to individual height and we used right brachial-to-right ankle baPWV. The validity of the device has been confirmed and the reproducibility of baPWV has been published (13).

We simultaneously measured BP and HR with baPWV in the supine position using the same device. Pulse pressure (PP) and mean arterial pressure (MAP) were calculated according to the formula: PP = SBP − DBP, and MAP = DBP + PP/3, respectively.

Statistical Analysis

The characteristics between healthy normotensives and controlled hypertensives were compared using the student's t-test for continuous variables and the χ^2-test for categorical variables.

For the 491 healthy normotensives, correlations between baPWV and various parameters were calculated. Multivariate stepwise regression analyses were used to evaluate which of linear, quadratic, and exponential functions optimally described the relationships between baPWV and age, and between baPWV and MAP. Covariates entered into the stepwise analysis included the variables that were significantly associated with PWV according to the univariate analysis. To construct a nomogram for theoretical baPWV, a multivariate stepwise regression analysis was performed using terms that described the optimal relationship between baPWV and age, and MAP. The upper limit of the 95% confidence interval (CI) of the theoretical baPWV value was calculated and we constructed a nomogram of the upper limit of baPWV.

To assess the applicability of the nomogram, we calculated the PWV index for each individual (16). Briefly, the PWV index was obtained by subtracting the theoretical baPWV from the measured baPWV. The PWV index was compared between 491 normotensive and 83 controlled hypertensive individuals and between subjects with and without smoking in controlled hypertensives after adjusted for confounding factors. We also examined the optimal cut-off point in the PWV index to distinguish controlled hypertensives from normotensives, using the receiver-operator characteristic (ROC) curve.

All statistical analyses were performed using SPSS software version 11.0 (SPSS Inc., Chicago IL, USA). A value of P <0.05 represented statistical significance.

RESULTS

The clinical characteristics of healthy normotensives and controlled hypertensives are given in Table 1.

Figure 1 shows the relationship between age and baPWV in the 491 healthy normotensives. BaPWV increased with age and in a nonlinear manner, being much more prominent in individuals over 50 years of age. The mean + SD, mean + 2 SDs, and 95th percentile values of baPWV in this population were 1607, 1844, and 1848 cm/sec, respectively.

Table 2 shows correlations between baPWV and various parameters. BaPWV was significantly and positively correlated with age and BP. Among the BP components, the correlation between MAP and baPWV was the closest, with a correlation coefficient of 0.49. The HR was also positively correlated with baPWV. Males had a higher baPWV than females (1,416 ± 232 vs. 1,347 ± 236 cm/sec, P = 0.002). Participants who regularly consumed alcohol had a significantly lower PWV than anyone else (1334 ± 220 vs. 1393 ± 244

Table 1. Clinical characteristics of the study population

	Healthy Normotensives (n = 491)	Controlled Hypertensives (n = 83)
Age (y)	55.9 ± 12.4	68.0 ± 7.9***
Gender (men/women)	169/322	34/49
SBP (mmHg)	123.2 ± 10.0	129.1 ± 7.7***
DBP (mmHg)	75.9 ± 6.8	78.9 ± 5.6***
MAP (mmHg)	92.9 ± 8.3	98.6 ± 5.5***
PP (mmHg)	47.3 ± 7.1	50.2 ± 8.5**
HR (mmHg)	66.2 ± 9.2	66.1 ± 9.6
baPWV (cm/sec)	1371 ± 237	1658 ± 236***
BMI (kg/m^2)	23.2 ± 2.8	24.1 ± 3.0**
Total cholesterol (mg/dl)	191.0 ± 27.5	193.4 ± 28.6
HDL cholesterol (mg/dl)	59.8 ± 15.5	57.7 ± 14.9
HbA_{1c} (%)	4.9 ± 0.4	5.0 ± 0.4*
Smoking habit (%)	17.9	15.7
Alcohol habit (%)	38.3	47.0

Abbreviations: SBP - systolic blood pressure; DBP - diastolic blood pressure; MAP - mean arterial pressure; PP - pulse pressure; HR - heart rate; bpm - beats per minute; baPWV - brachial-ankle pulse wave velocity; BMI - body mass index; HDL - high-density lipoprotein; HbA_{1c} - hemoglobin A_{1c}.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, vs. healthy normotensives.
Data are expressed as the mean ± SD.

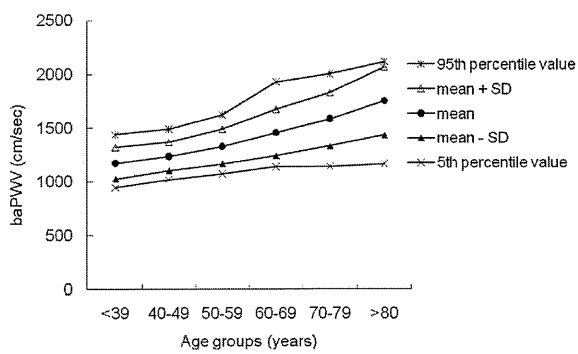

Figure 1. The relations of age to baPWV in 491 healthy normotensives.

cm/sec, P = 0.007). The PWV between those with a smoking habit and others did not significantly differ (1352 ± 198 vs. 1374 ± 244 cm/sec, P = 0.36).

We performed stepwise regression analysis to construct an equation for the theoretical PWV. The variables that were significantly associated with baPWV according to the bi-variate analysis (age, MAP, HR, gender, BMI, total cholesterol, HDL cholesterol, HbA_{1c}, and alcohol habit) were used as potential explanatory variables. Because the relationships between baPWV and age and MAP could be nonlinear, we added a nonlinear term for age and MAP to the equation. We chose a quadratic term rather than an exponential term, since the quadratic functions described the relationship with baPWV better than the exponential function (data not shown).

Table 2. Correlation of baPWV and various parameters in 491 healthy normotensives

	r	P
Age (y)	0.622	<0.001
SBP (mmHg)	0.445	<0.001
DBP (mmHg)	0.396	<0.001
MAP (mmHg)	0.488	<0.001
PP (mmHg)	0.248	<0.001
HR (bpm)	0.161	<0.001
BMI (kg/m^2)	0.095	0.035
Total cholesterol (mg/dl)	0.152	0.001
HDL cholesterol (mg/dl)	−0.134	0.003
HbA_{1c} (%)	0.232	<0.001

Abbreviations: r - Pearson correlation coefficient; baPWV - brachial-ankle pulse wave velocity; SBP - systolic blood pressure; DBP - diastolic blood pressure; MAP - mean arterial pressure; PP - pulse pressure; HR - heart rate; bpm - beats per minute; BMI - body mass index; HDL - high-density lipoprotein; HbA_{1c} - hemoglobin A_{1c}.

Table 3. Multiple stepwise regression analysis to construct nomograms

	β	t	P
Nomogram for calculation of a theoretical baPWV value* ($R^2 = 0.53$)			
Age^2 (y^2)	1.26	4.46	<0.001
Age (y)	−0.72	−2.53	0.012
MAP^2 (mmHg^2)	0.32	9.66	<0.001
HR (bpm)	0.15	4.77	<0.001
Gender (1 men; 0 women)	0.07	2.28	0.023
Intercept		4.42	<0.001
Nomogram for calculation of the upper limit of normal baPWV**			
Age^2 (y^2)	1.75	981.47	<0.001
Age (y)	−1.02	−569.45	<0.001
MAP^2 (mmHg^2)	0.48	132.86	<0.001
MAP (mmHg)	−0.04	−10.22	<0.001
HR (bpm)	0.21	1047.94	<0.001
Gender (1 men; 0 women)	0.10	503.20	<0.001
Intercept		324.67	<0.001

Abbreviations: β - standardized partial regression coefficient; baPWV - brachial-ankle pulse wave velocity; MAP - mean arterial pressure; HR - heart rate; bpm - beats per minute.
*Factors excluded from the model: MAP, BMI, total cholesterol, HDL cholesterol, HbA_{1c}, alcohol habit.
**Factors excluded from the model: BMI, total cholesterol, HDL cholesterol, HbA_{1c}, alcohol habit.

When both linear and quadratic terms for age and MAP were thus entered into the models, age^2, age, MAP^2, HR, gender were independently correlated with baPWV, accounting for 53.0% of the variance (Table 3). Other factors were not significant determinants of baPWV. Hence, the theoretical baPWV was calculated from the following equation:

Theoretical baPWV (cm/sec)

$$= 0.21 \times \text{age}^2(\text{years}^2) - 13.73 \times \text{age (years)}$$

$$+ 0.05 \times \text{MAP}^2\ (\text{mmHg}^2)$$

$$+ 3.95 \times \text{HR (bpm)} + 36.49 \times \text{gender}$$

$$(1\ \text{male};\ 0\ \text{female}) + 733.$$

The individual normal upper limit of baPWV was similarly calculated using the following equation:

$$\text{Upper limit of normal baPWV (cm/sec)}$$

$$= 0.22 \times \text{age}^2\ (\text{years}^2) - 14.22 \times \text{age (years)}$$

$$+ 0.05 \times \text{MAP}^2\ (\text{mmHg}^2) - 0.76 \times \text{MAP (mmHg)}$$

$$+ 4.00 \times \text{HR (bpm)}$$

$$+ 37.26 \times \text{gender (1 male; 0 female)} + 1100.$$

Assessment of Nomogram Applicability

The nomogram of a theoretical baPWV was applied to all the participants, and a PWV index was calculated for each individual. The PWV index (measured baPWV – theoretical baPWV) was significantly greater in patients with controlled hypertension than healthy normotensive subjects even after adjusted for confounding factors (95.3 ± 18.1 vs. 1.1 ± 7.4 cm/sec, $P < 0.001$). The PWV index was higher in 13 smokers (148.4 ± 54.6 cm/sec) than 70 nonsmokers (92.6 ± 21.5 cm/sec, $p = 0.36$) after adjusted for confounding factors. According to the ROC curve, cut-off point yielding maximal sensitivity plus specificity to distinguish was 74 cm/sec. Sensitivity and specificity using this cut-off point was 55.4% and 72.0%, respectively.

DISCUSSION

In the present study, we constructed a nomogram for theoretical PWV considering the effects of age, BP, HR, and gender. A definite cut-off value of PWV is not always appropriate for all subjects because PWV depends on various physiological factors (12, 15, 21), although some reports, including the recent ESH-ESC guidelines (22), proposed a cut-off value. Therefore, we chose a nomogram rather than a cut-off value to determine the normalcy of PWV. The PWV index, namely, a difference between measured and theoretical PWV, was significantly greater in patients with controlled hypertension than healthy normotensive subjects.

Blacher et al. (16) and Yamashina et al. (23) have also constructed a nomogram with which to calculate theoretical PWV. Blacher et al. (16) measured PWV between the carotid and femoral arteries. Because their study subjects were nonuremic and included outpatients seen in consultation, members of the paramedical and medical staff, and patients hospitalized in departments other than nephrology, the theoretical PWV calculated on the basis of their nomogram is probably not applicable to the general population. In the present study, we measured PWV between the brachial and ankle regions. Measuring baPWV using pressure cuffs wrapped on the brachial and ankle is a simple and noninvasive method for assessing arterial stiffness. A recent study (24) demonstrated that baPWV were significantly and positively correlated with cfPWV ($r = 0.73$) and baPWV and cfPWV were similarly associated with risk factors for coronary artery disease. It has been reported that baPWV had a predictive power for the mortality of patients with severe renal disease (25, 26). Yamashina et al. (23) represented the relationships between age and baPWV at each SBP level and between SBP and baPWV at each age class as a quadratic curve. This is consistent with the findings of ours and others (12, 15, 21, 23) that the relationships of baPWV with age and BP could be represented by quadratic function. However, despite this similarity, coefficients of each PWV determinant were somewhat different between the studies. One possible explanation for this difference could be the inclusion of HR as a determinant of baPWV in our study but not in the previous study (23). We included HR because a substantial number of previous studies have shown an important effect of HR on PWV (13, 14). Recently, Tomiyama et al. (27) also reported that HR was cross-sectionally and prospectively associated with changes in baPWV in a large sample prospective follow-up study. Therefore, it would be better to take into consideration of HR to construct a nomogram for theoretical baPWV. Alternatively, the difference might be attributable to a difference in study population; our study comprised a relatively older, rural general population with a mean age of 56 years, whereas the previous study (23) comprised a younger urban population with a mean age of 46 years.

Blacher et al. (16) originally introduced the PWV index, which was obtained by subtracting a theoretical PWV from a measured PWV, thus reflecting pathologic, rather than physiologic change in arterial stiffness. Consistent with their suggestion, the last part of our results showed that the measured baPWV in patients with controlled hypertension was higher than the theoretical baPWV. This result indicates that the "arterial age" is higher than chronological age in these patients. Moreover, we demonstrated that the PWV index was greater in the controlled hypertensive patients than healthy normotensive subjects. The PWV index was also higher in smokers than nonsmokers. Therefore, the greater PWV index may ensure the existence of severe arterial change. Although we could not evaluate the influence of hypertension history on the PWV index, this finding may suggest that, even if being controlled, long-term history of hypertension increases inherent arterial stiffness. Vergrand et al. (28) previously reported that in spite of the same BP level, treated

hypertensive patients had increased wave reflection and a higher PWV than normotensive subjects. This might be explicable by irreversible structural degeneration of arterial media before the initiation of treatment, or by nonhemodynamic factors relating to arterial stiffening (29). In the present study, we calculated an optimal cut-off point in the PWV index to distinguish controlled hypertensives from normotensives. Blacher et al. (16) previously reported that 1.63 and 0.68 m/sec was the cut-off point in the PWV index for increased risk of cardiovascular and overall death in 242 patients with end-stage renal disease. It is expected that the cut-off point in the PWV index to predict cardiovascular disease mortality and morbidity from the Ohasama study population in the near future.

In conclusion, we constructed a nomogram for theoretical PWV, in which various physiological factors were taken into account. The PWV index based on this nomogram might be applicable not only to general screening but also to clinical practice for evaluating individual inherent arterial stiffness. Future studies are required to clarify whether the PWV index has more potential than conventional markers to assess individual cardiovascular risk and provide effective preventive strategies.

ACKNOWLEDGMENTS

We are grateful to the staff members of the Iwate Prefectural Stroke Registry and to the public health nurses in Ohasama for their valuable support of this project.

The work was supported by Grants for Scientific Research (15790293, 16590433, 17790381, 17790381, 18390192, 18590587, 19590929, and 19790423) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; a Grant-in-Aid (H17-Kenkou-007, H18-Junkankitou [Seishuu]-Ippan-012, and H20-Junkankitou [Seishuu]-Ippan-009, 013) from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; a Grant-in-Aid for Japan Society for the Promotion of Science (JSPS) fellows (16.54041, 18.54042, 19.7152, 20.7198, 20.7477, and 20.54043), Tokyo, Japan; Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; Japan Atherosclerosis Prevention Fund; the Uehara Memorial Foundation; the Takeda Medical Research Foundation; National Cardiovascular Research Grants; and Biomedical Innovation Grants.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

[1] Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke* 2003;34:1203–1206.

[2] Blacher J, Asmar R, Djane S, London GM, Safer ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1990;33:1111–1117.

[3] Watabe D, Hashimoto J, Hatanaka R, Hanazawa T, Ohba H, Ohkubo T, Kikuya M, Totsune K, Imai Y. Electrocardiographic left ventricular hypertrophy and arterial stiffness: The Ohasama study. *Am J Hypertens* 2006;19:1199–1205.

[4] London GM, Guerin AP. Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am Heart J* 1999;138:S220–S224.

[5] O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 2007;50:1–13.

[6] Hashimoto J, O'Rourke MF. Is arterial stiffness better than blood pressure in predicting cardiovascular risk?*Curr Cardiovasc Risk Rep* 2008;2:133–140.

[7] O'Rourke MF, Safer ME. Relationship between aortic stiffening and microvascular disease in brain and kidney. *Hypertension* 2005;46:200–204.

[8] Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac MA, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995;26:485–490.

[9] Hashimoto J, Chonan K, Aoki Y, Nishimura T, Ohkubo T, Hozawa A, Suzuki M, Matsubara M, Michimata M, Araki T, Imai Y. Pulse wave velocity and the second derivative of the finger photoplethysmogram in treated hypertensive patients: their relationship and associating factors. *J Hypertens* 2002;20:2415–2422.

[10] Najjar SS, Scuteri A, Lakatta EG. Arterial aging: Is it an immutable cardiovascular risk factor? *Hypertension* 2005;46: 454–462.

[11] Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation* 1985;71:202–210.

[12] Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The Framingham Heart Study. *Hypertension* 2004;43: 1239–1245.

[13] Munakata M, Ito N, Nunokawa T, Yoshinaga K. Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. *Am J Hypertens* 2003;16:653–657.

[14] Haesler E, Lyon X, Pruvot E, Kappenberger L, Hayoz D. Confounding effects of heart rate on pulse wave velocity in paced patients with a low degree of atherosclerosis. *J Hypertens* 2004;22:1317–1322.

[15] Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, Hori S, Yamamoto Y, Doba N, Hinohara S. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement-a survey of 12517 subjects. *Atherosclerosis* 2003;166:303–309.

[16] Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int* 2003;63:1852–1860.

[17] Hashimoto J, Watabe D, Kimura A, Takahashi H, Ohkubo T, Totsune K, Imai Y. Determinants of the second derivative of the finger photoplethysmogram and brachial-ankle pulse-wave velocity: The Ohasama study. *Am J Hypertens* 2005;18: 477–485.

[18] Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, Tanaka H. Brachial-ankle pulse wave velocity: an index of central arterial stiffness? *J Hum Hypertens* 2005;19:401–406.

[19] Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002;25: 359–364.

[20] Imai Y, Nagai K, Sakuma M, Sakuma H, Nakatsuka H, Satoh H, Minami N, Munakata M, Hashimoto J, Yamagishi T. Ambulatory blood pressure of adults in Ohasama, Japan. *Hypertension* 1993;22:900–912.

[21] McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity The Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005;46:1753–1760.

[22] European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2007 Guiidelines for the Management of Arterial Hypertension. *Eur Heart J* 2007;28: 1462–1536.

[23] Yamashina A, Tomiyama H, Arai T, Koji Y, Yambe M, Motobe H, Glunizia Z, Yamamoto Y, Hori S. Nomogram of the relation of brachial-ankle pulse wave velocity with blood pressure. *Hypertens Res* 2003;26:801–806.

[24] Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T. Comparison between carotid- femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *J Hypertens* 2009;27:2022–2027.

[25] Kitahara T, Ono K, Tsuchida A, Kawai H, Shinohara M, Ishii Y, Koyanagi H, Noguchi T, Matsumoto T, Sekihara T, Watanabe Y, Kanai H, Ishida H, Nojima Y. Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. *Am J Kidney Dis* 2005;46:688–696.

[26] Morimoto S, Yurugi T, Aota Y, Sakuma T, Jo F, Nishikawa M, Iwasaka T, Maki K. Prognostic significance of ankle-brachial index, brachial-ankle pulse wave velocity, flow-mediated dilation, and nitroglycerin-mediated dilation in end-stage renal disease. *Am J Nephrol* 2009;30: 55–63.

[27] Tomiyama H, Hashimoto H, Tanaka H, Matsumoto C, Odaira M, Yamada J, Yoshida M, Shiina K, Nagata M, Yamashina A; baPWV/cfPWV Collaboration Group. Synergistic relationship between changes in the pulse wave velocity and changes in the heart rate in middle-aged Japanese adults: a prospective study. *J Hypertens.* 2010;28:687–694.

[28] Vergnaud AC, Protogerou AD, Blacher J, Safar ME. From "optimal" to "borderline" blood pressure in subjects under chronic antihypertensive therapy. *J Hypertens* 2008;26: 138–144.

[29] Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. London: A Hodder Arnold Publication, 2005.

blood

2011 117: 2113-2120
Prepublished online November 24, 2010;
doi:10.1182/blood-2010-05-285502

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

Saiko Kurosawa, Takuhiro Yamaguchi, Shuichi Miyawaki, Naoyuki Uchida, Heiwa Kanamori, Kensuke Usuki, Takuya Yamashita, Masato Watanabe, Kazuaki Yakushiji, Shingo Yano, Yuichiro Nawa, Jun Taguchi, Jin Takeuchi, Junji Tomiyama, Yuko Nakamura, Ikuo Miura, Yoshinobu Kanda, Yoichi Takaue and Takahiro Fukuda

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.

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

Saiko Kurosawa,[1] Takuhiro Yamaguchi,[2] Shuichi Miyawaki,[3] Naoyuki Uchida,[4] Heiwa Kanamori,[5] Kensuke Usuki,[6] Takuya Yamashita,[7] Masato Watanabe,[8] Kazuaki Yakushiji,[9] Shingo Yano,[10] Yuichiro Nawa,[11] Jun Taguchi,[12] Jin Takeuchi,[13] Junji Tomiyama,[14] Yuko Nakamura,[15] Ikuo Miura,[16] Yoshinobu Kanda,[17] Yoichi Takaue,[1] and Takahiro Fukuda[1]

[1]Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, Japan; [2]Clinical Data Management Division, University of Tokyo, Tokyo, Japan; [3]Metropolitan Ohtsuka Hospital, Tokyo, Japan; [4]Toranomon Hospital, Tokyo, Japan; [5]Kanagawa Cancer Center, Kanagawa, Japan; [6]NTT Kanto Medical Center, Tokyo, Japan; [7]Metropolitan Komagome Hospital, Tokyo, Japan; [8]Yamada Hospital, Gifu, Japan; [9]Kurume University, Fukuoka, Japan; [10]Jikei University, Tokyo, Japan; [11]Ehime Prefectural Central Hospital, Ehime, Japan; [12]Nagasaki University, Nagasaki, Japan; [13]Nihon University, Tokyo, Japan; [14]Metropolitan Bokutoh Hospital, Tokyo, Japan; [15]Dokkyo Medical University, Tochigi, Japan; [16]St Marianna University School of Medicine Hospital, Kanagawa, Japan; and [17]Saitama Medical Center, Jichi Medical University, Saitama, Japan

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.

Submitted May 14, 2010; accepted November 10, 2010. Prepublished online as *Blood* First Edition paper, November 24, 2010; DOI 10.1182/blood-2010-05-285502.

An Inside *Blood* analysis of this article appears at the front of this issue.

The online version of this article contains a data supplement.

Presented at the 51st annual meeting of the American Society of Hematology in New Orleans, LA, December 6, 2009.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

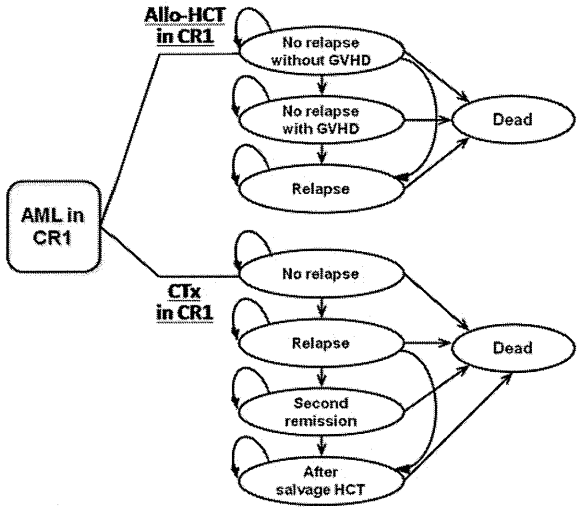

Figure 1. Markov decision model. Markov model that compares allo-HCT in CR1 and chemotherapy in CR1 is shown. Possible health states for each of the 2 groups are indicated in circles. Arrows indicate possible transitions between states. CR1 indicates first complete remission; allo-HCT, allogeneic hematopoietic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

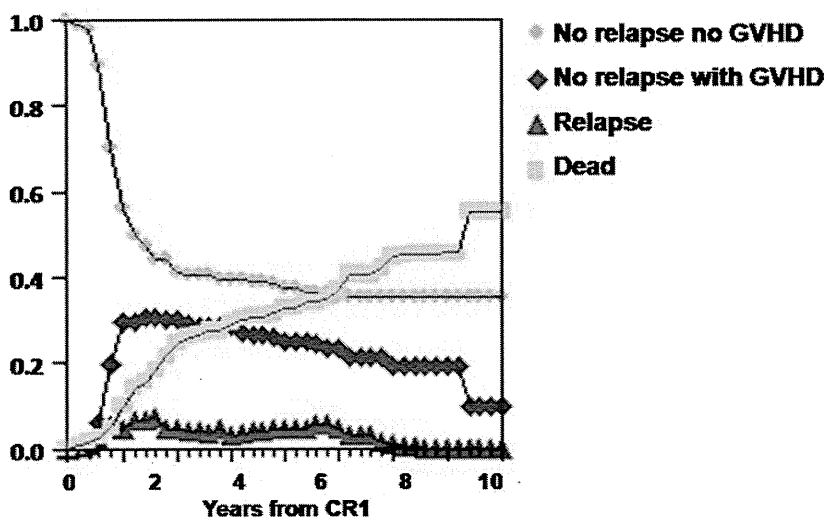

Figure 2. Distribution of patients in each health state. Distribution of patients with intermediate-risk AML in each health state is shown. Transition probabilities between the states were calculated for each subgroup with the use of the database. The probabilities of state transition were allowed to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

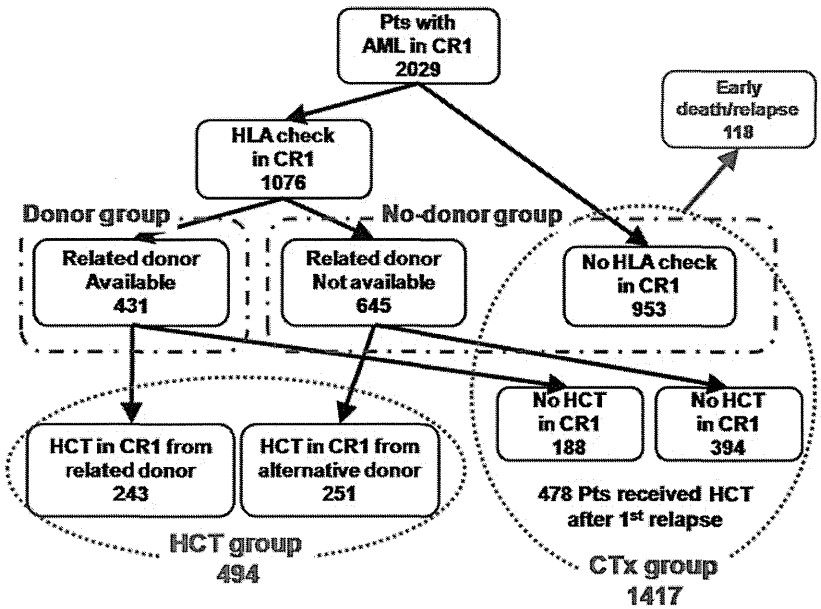

Figure 3. Patient flow. The flow of HLA check, donor availability, and actual application of allo-HCT in CR1 are shown. Among the total of 2029 patients with AML in CR1, 494 received allo-HCT in CR1 and were included in the HCT group. Among the remaining 1535 patients, 118 patients who died or relapsed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

		HLA check in CR1 (n = 1076)			
Characteristics	No HLA check in CR1	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

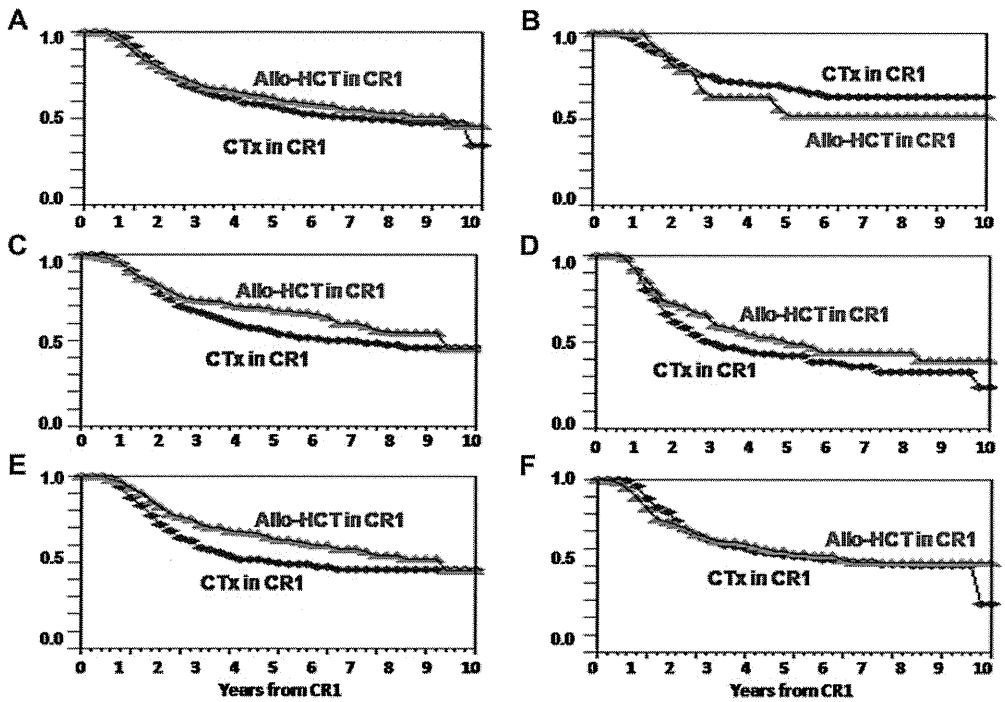

Figure 4. Survival curves of allo-HCT versus CTx by TreeAge. The overall survival curves of the HCT and CTx groups depicted by TreeAge Pro 2009 in (A) total patients, (B) SWOG favorable-risk group, (C) intermediate-risk group, (D) unfavorable-risk group, (E) donor group, and (F) no-donor group. allo-HCT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

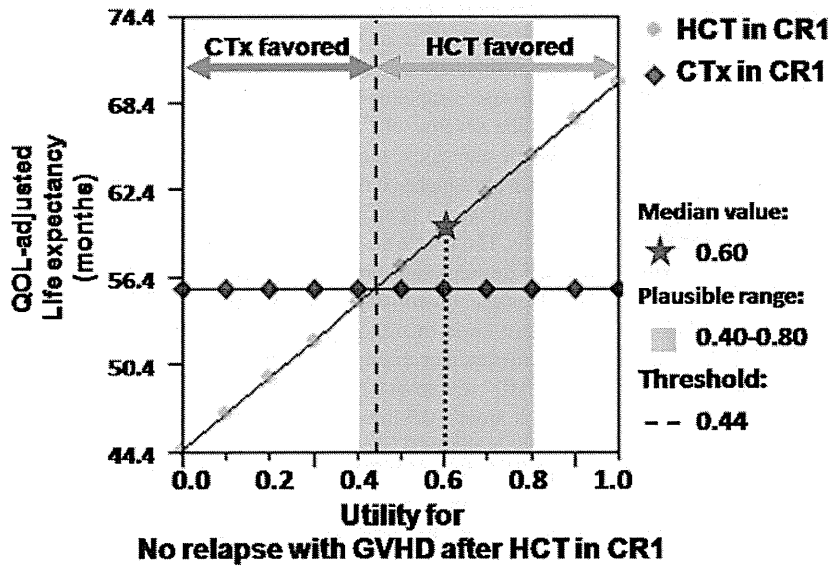

Figure 5. One-way sensitivity analysis. One-way sensitivity analysis for the utility of the state "No relapse with GVHD" after allogeneic transplantation in CR1 among patients with intermediate-risk AML is shown. The green dot represents the QOL-adjusted life expectancy when allo-HCT was performed in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

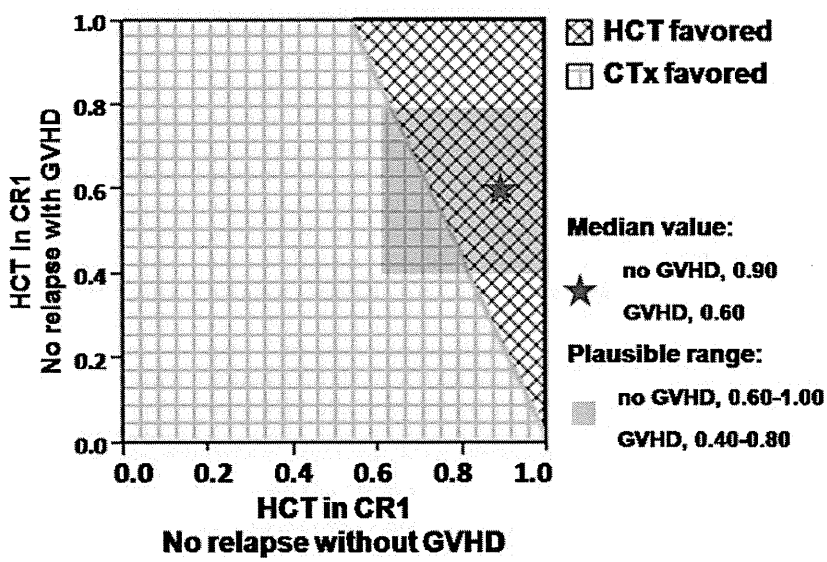

Figure 6. Two-way sensitivity analysis. Two-way sensitivity analysis for the utilities of the states "No relapse without GVHD" and "No relapse with GVHD." The blue area represents the range in which HCT is favored. The green area represents the range in which CTx is favored. Although the median value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

Acknowledgments

We thank Dr Corey Cutler and Dr John Koreth for helpful discussion.

This work was supported by grants from the Japanese Ministry of Health, Labor and Welfare and the Advanced Clinical Research Organization.

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.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Takahiro Fukuda, Stem Cell Transplantation Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan; e-mail: tafukuda@ncc.go.jp.

References

1. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. *N Engl J Med.* 1999;341(14):1051-1062.
2. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood.* 2000;96(13):4075-4083.
3. Suciu S, Mandelli F, de Witte T, et al. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMAAML-10 trial. *Blood.* 2003;102(4):1232-1240.
4. Jourdan E, Boiron JM, Dastugue N, et al. Early allogeneic stem-cell transplantation for young adults with acute myeloblastic leukemia in first complete remission: an intent-to-treat long-term analysis of the BGMT experience. *J Clin Oncol.* 2005;23(30):7676-7684.
5. Burnett AK, Wheatley K, Goldstone AH, Stevens R, Hann I, Hills RK. Long-term results of the MRC AML10 trial. *Clin Adv Hematol Oncol.* 2006;4(6):445-451.
6. Cornelissen JJ, van Putten WL, Verdonck LF, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? *Blood.* 2007;109(9):3658-3666.
7. Basara N, Schulze A, Wedding U, et al. Early related or unrelated haematopoietic cell transplantation results in higher overall survival and leukaemia-free survival compared with conventional chemotherapy in high-risk acute myeloid leukaemia patients in first complete remission. *Leukemia.* 2009;23(4):635-640.
8. Schlenk RF, Benner A, Hartmann F, et al. Risk-adapted postremission therapy in acute myeloid leukemia: results of the German multicenter AML HD93 treatment trial. *Leukemia.* 2003;17(8):1521-1528.
9. Sakamaki H, Miyawaki S, Ohtake S, et al. Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study. *Int J Hematol.* 2010;91(3):471-477.
10. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA.* 2009;301(22):2349-2361.
11. Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. Primer on medical decision analysis: part 1—getting started. *Med Decis Making.* 1997;17(2):123-125.
12. Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: part 5—working with Markov processes. *Med Decis Making.* 1997;17(2):152-159.
13. Lee SJ, Kuntz KM, Horowitz MM, et al. Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: a decision analysis. *Ann Intern Med.* 1997;127(12):1080-1088.
14. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood.* 2004;104(2):579-585.
15. Sung L, Buckstein R, Doyle JJ, Crump M, Detsky AS. Treatment options for patients with acute myeloid leukemia with a matched sibling donor: a decision analysis. *Cancer.* 2003;97(3):592-600.
16. Martin PJ, Storer BE, Rowley SD, et al. Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. *Blood.* 2009;113(21):5074-5082.
17. Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood.* 2004;104(12):3501-3506.
18. Hegenbart U, Niederwieser D, Sandmaier BM, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol.* 2006;24(3):444-453.
19. Appelbaum FR. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia when a matched related donor is not available. *Hematology Am Soc Hematol Educ Program.* 2008;2008:412-417.
20. Lee SJ, Joffe S, Kim HT, et al. Physicians' attitudes about quality-of-life issues in hematopoietic stem cell transplantation. *Blood.* 2004;104(7):2194-2200.
21. Lee SJ, Kim HT, Ho VT, et al. Quality of life associated with acute and chronic graft-versus-host disease. *Bone Marrow Transplant.* 2006;38(4):305-310.
22. Pidala J, Anasetti C, Kharfan-Dabaja MA, Cutler C, Sheldon A, Djulbegovic B. Decision analysis of peripheral blood versus bone marrow hematopoietic stem cells for allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2009;15(11):1415-1421.
23. Pidala J, Anasetti C, Jim H. Quality of life after allogeneic hematopoietic cell transplantation. *Blood.* 2009;114(1):7-19.
24. Zittoun R, Suciu S, Watson M, et al. Quality of life in patients with acute myelogenous leukemia in prolonged first complete remission after bone marrow transplantation (allogeneic or autologous) or chemotherapy: a cross-sectional study of the EORTC-GIMEMA AML 8A trial. *Bone Marrow Transplant.* 1997;20(4):307-315.