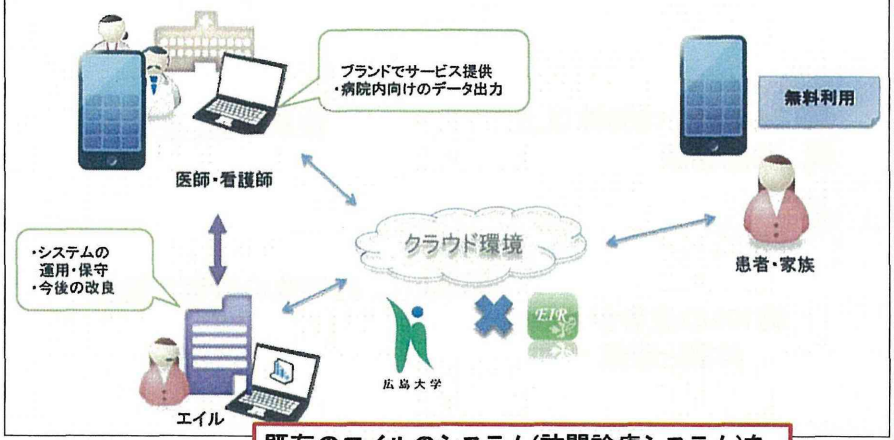
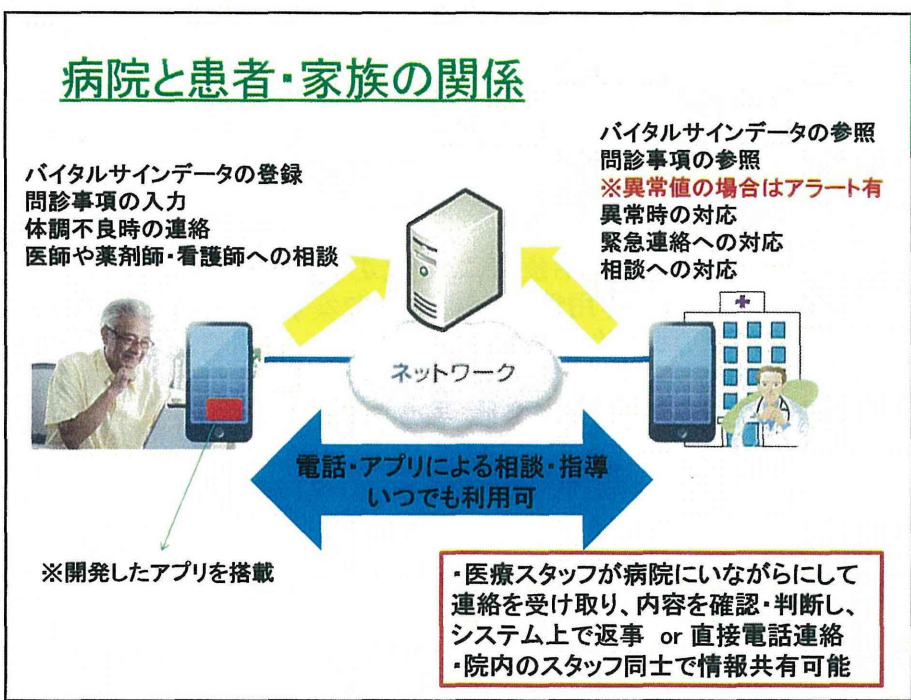
システムの概要



既存のエイルのシステム(訪問診療システム)を
ベースに外来化学療法用のシステムを構築
(Webページ、iPhoneアプリ)
運用・保守・改良

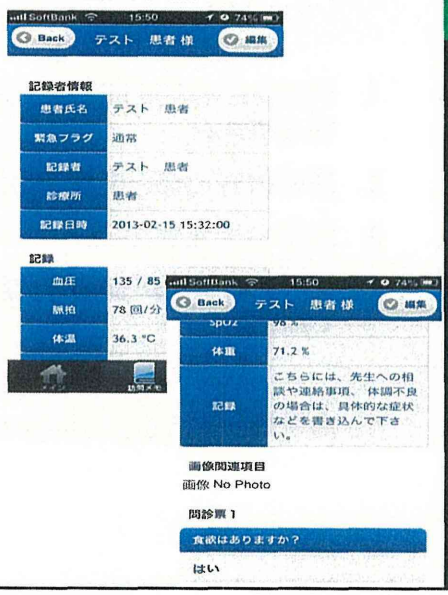
病院と患者・家族の関係



・医療スタッフが病院にいながらにして
連絡を受け取り、内容を確認・判断し、
システム上で返事　or 直接電話連絡
・院内のスタッフ同士で情報共有可能

WEBページ

スマートフォンアプリ



問診事項

Q1. 本日の体調はいかがですか？

(1)良い　(2)普通　(3)やや悪い　(4)悪い　(5)非常に悪い

⇒(4)または(5)：至急フラグ、(5)：緊急フラグ

Q2. 食事はとれていますか？

(1)以前とほぼ同様　(2)やや少ない（7-8割）　(3)半分程度

(4)少量のみ（2-3割）　(5)ほとんど食べられていない

⇒(5)：至急フラグ

Q3. 身体のどこかに痛みがありますか？

(1)はい　(2)いいえ

→(1)はいの場合　部位（　）

強さ（スケールで表してください）10段階から選ぶ

⇒スケール7以上：至急フラグ

システムの利点

1. 重篤な副作用の軽減につながり、治療成績の向上に寄与できる。
2. 患者の安心感と満足度の向上につながる。
3. 医療の安全性の向上につながる。
4. システム構築が安価で、汎用性と実現可能性が極めて高い。
5. 病院間、病院と地域医療の連携に利用できる。

今後の課題

1. 医療機関内でのシステムの運用体制整備
2. 開発したシステムを用いた臨床研究の評価の難しさ
3. 個人情報に配慮した上での院内の電子診療録との連動
4. 高齢患者などスマートフォンの使用になれていない患者・家族に対する適応のための工夫

   → 健康医療機器との連動

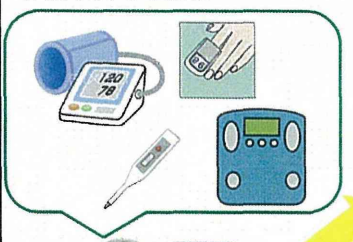
   音声認識システムの使用
5. 対象患者の疾患や治療毎のシステムの対応

   →問診事項や評価項目の設定、情報提供

課題解決にむけて

・患者が在宅生活を基盤にしながら健康医療機器による自己管理
・病院で生体情報測定データを確認
・異常時の対応
（システム上で対応　or 直接電話連絡）
・院内・院外のスタッフが情報共有可能

健康医療機器による自己管理
（生体情報測定データの登録）
体調不良時の連絡



健康医療機器による
生体情報測定データの参照
※異常値の場合はアラート有
異常時の対応

アプリケーションを用いた
生体情報測定データのモニタリング

※開発したアプリを搭載

※開発したアプリを搭載

音声認識・解析技術応用

1）問診票の音声ガイド／音声入力
　①音声合成技術を用いた問診票の質問読み上げ
　②患者様の音声による回答、問診票への登録
　③イレギュラーな回答に対する柔軟な応答、および医療関連用語など重要な情報の拾い上げ

2）音声操作によるメール発信
　①音声によるメーラーソフトの起動
　②音声による宛先/タイトル/本文の入力
　③音声による本文の読み上げ、確認
　④上記③の修正
　⑤音声によるメール発信指示

3）FAQ音声検索アシスタント
　①会話をしながら欲しい情報の高速検索
　②検索結果の音声でのお知らせ

II. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

総合報告書 ／ 刊行一覧

著者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
Oshima K, Takahashi W, Asano-Mori Y, Izutsu K, Takahashi T, Arai Y, Nakagawa Y, Usuki K, Kurokawa M, Suzuki K, Mitani K, Kanda Y.	Intensive chemotherapy for elderly patients with acute myelogeneous leukemia: a propensity score analysis by the Japan Hematology and Oncology Clinical Study Group (J-HOCS).	Ann Hematol.	91(10)	1533-9	2012
Oshima K, Kanda Y, Nanya Y, Tanaka M, Nakaseko C, Yano S, Fujisawa S, Fujita H, Yokota A, Takahashi S, Kanamori H, Okamoto S; Kanto Study Group for Cell Therapy.	Allogeneic hematopoietic stem cell transplantation for patients with mildly reduced renal function as defined based on creatinine clearance before transplantation.	Ann Hematol.	92(2)	255-60	2013
Oshima K, Kanda Y, Kako S, Ohno K, Kishino S, Kurokawa M.	Pharmacokinetics of micafungin in patients undergoing allogeneic hematopoietic stem cell transplantation.	Transpl Infect Dis.	15(3)	323-7	2013

Ann Hematol (2012) 91:1533–1539
DOI 10.1007/s00277-012-1487-1

ORIGINAL ARTICLE

Intensive chemotherapy for elderly patients with acute myelogeneous leukemia: a propensity score analysis by the Japan Hematology and Oncology Clinical Study Group (J-HOCS)

Kumi Oshima · Wataru Takahashi · Yuki Asano-Mori · Koji Izutsu · Tsuyoshi Takahashi · Yukihiro Arai · Yasunori Nakagawa · Kensuke Usuki · Mineo Kurokawa · Kenshi Suzuki · Kinuko Mitani · Yoshinobu Kanda

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Abstract The prognosis of acute myelogenous leukemia (AML) in the elderly patients is extremely poor. Although several previous studies have suggested that intensive chemotherapy is associated with a better prognosis, there may have been a selection bias. Therefore, we retrospectively evaluated the impact of intensive chemotherapy for AML in the elderly by stratifying patients according to a propensity score. Eighty-one AML patients aged 70 years or more were included in this study. Patients with acute promyelocytic leukemia were not included. A propensity score for the use of intensive chemotherapy was calculated from four factors at diagnosis. Forty-five patients received intensive chemotherapy, whereas 36 received low-dose or no chemotherapy. We stratified the patients into quartiles based on the propensity score. The numbers of patients in the first, second, third, and forth quartiles who received intensive chemotherapy were 5 of 21, 10 of 20, 12 of 20, and 18 of 20, respectively. A stratified log-rank test showed significantly better overall survival in the intensive chemotherapy group (P=0.0088). Especially, in the combined second and third quartiles, which showed an equal tendency for intensive and non-intensive strategies; overall survival at 3 years was 37.5 % for the intensive chemotherapy group and 13.0 % for the non-intensive chemotherapy group (P=0.0022). A conventional multivariate analysis confirmed that intensive chemotherapy was beneficial (hazard ratio 0.50, 95 % confidence interval 0.27–0.93, P=0.028). In conclusion, intensive chemotherapy may prolong overall survival in elderly AML patients who are considered to be able to tolerate such treatment based on factors at diagnosis.

Keywords AML · Elderly · Intensive chemotherapy · Propensity score

K. Oshima · Y. Kanda (✉)
Division of Hematology, Saitama Medical Center,
Jichi Medical University,
Saitama, Japan
e-mail: ycanda-tky@umin.ac.jp

W. Takahashi · Y. Arai · K. Mitani
Department of Hematology,
Dokkyo University School of Medicine,
Tochigi, Japan

Y. Asano-Mori · Y. Nakagawa · K. Suzuki
Department of Oncology and Hematology,
Japanese Red Cross Medical Center,
Tokyo, Japan

K. Izutsu · K. Usuki
Division of Hematology, NTT Kanto Medical Center,
Tokyo, Japan

T. Takahashi · M. Kurokawa
Department of Hematology and Oncology,
University of Tokyo Hospital,
Tokyo, Japan

Introduction

The incidence of acute myelogenous leukemia (AML) increases with age [1, 2]. In addition, an increasing age is an adverse prognostic factor of AML [3–5]. AML in elderly patients is characterized by an increased incidence of unfavorable AML-related features including cytogenetic and

molecular genetic changes in leukemic cells, the existence of prior myelodysplastic syndrome (MDS) or myeloproliferative neoplasm, and previous cytotoxic therapy for another disorder (therapy-related AML) [6–8]. However, older patients may have a worse outcome than younger patients even in the absence of these risk factors [8]. Elderly patients tend to have comorbidities and a poor performance status (PS) at diagnosis [1]. In addition, the number of organ dysfunctions increases with age [9]. Therefore, elderly patients are thought to be less able to tolerate intensive chemotherapy. In fact, comorbidities and poor PS have been associated with the prognosis of elderly AML patients [5, 6, 10, 11]. In a recent study of patients older than 60 years of age, the baseline comorbidity score according to the hematopoietic cell transplantation comorbidity index was predictive of an early death and overall survival [5].

With regard to the treatment of elderly AML, several studies have suggested that intensive chemotherapy is beneficial in terms of remission induction and overall survival [4, 12]. However, these data should be interpreted with caution, since there may have been a selection bias. In addition, the treatment-related mortality rate of 10–40 % is a significant limitation to the application of intensive chemotherapy to elderly patients. Recently, a propensity score, that is the conditional probability of receiving a treatment given the covariates, became widely used to adjust for a selection bias in observational studies [13].Therefore, in this study, we retrospectively evaluated the impact of intensive chemotherapy for AML in the elderly by stratifying patients according to the propensity score to receive intensive chemotherapy.

Patients and methods

Study population

The study population consisted of 81 AML patients aged 70 years or more who were diagnosed for the first time between January 1994 and December 2004 at five hospitals participating in the Japan Hematology and Oncology Clinical Study Group. Patients with acute promyelocytic leukemia were not included.

Data collection

Patients' data were collected from their clinical records. The general condition of the patients was determined using the Eastern Cooperative Oncology Group (ECOG) PS at diagnosis. Cognitive ability was assessed based on the Hasegawa dementia scale [14]. Patients' comorbidities were assessed using Santariano's index as a reference [15]. In addition, the presence of infectious disease and hemorrhage at diagnosis were also evaluated as AML-related comorbidities. Treatments for AML were classified into four groups; a no-chemotherapy group, a low-dose chemotherapy group, a reduced-intensity chemotherapy group, and a standard chemotherapy group. The low-dose chemotherapy group included treatments with low-dose (40 mg/m^2/day or less) cytarabine-based chemotherapy such as low-dose cytarabine alone or low-dose cytarabine and aclarubicin with or without granulocyte colony-stimulating factor. Standard chemotherapy included induction chemotherapies similar to those that are used for younger patients (idarubicin plus cytarabine, daunorubicin plus cytarabine, mitoxantrone plus cytarabine, and idarubicin plus behenoyl cytarabine). Reduced-intensity chemotherapy was defined as being similar to standard chemotherapy but with a dose reduction to 50–70 % of the standard dose. However, in the following analyses, seven patients in the no-chemotherapy group and 29 patients in the low-dose chemotherapy group were combined into a non-intensive chemotherapy group, and the 45 patients in the other two groups were combine into an intensive chemotherapy group, since the no-chemotherapy and standard chemotherapy groups each contained very few patients. Treatment-related toxicities were evaluated using the Common Terminology Criteria for Adverse Events version 3.0.

Statistical considerations

The factors that were used to calculate the propensity score were selected from the following 12 factors at diagnosis: age, sex, ECOG-PS, cognitive function, coexistence of infectious complications, prior diagnosis of MDS, white blood cell count, hemoglobin level, peripheral blood blast percentage, serum creatinine level, serum total bilirubin level, and the institute where the patient was treated. Next, we deleted the factors from the logistic regression model in a stepwise manner based on the Akaike information criterion (AIC) and multicollinearity, since the number of patients was limited. Finally, the *C* statistic (area under the receiver operating characteristic curve) was evaluated to appraise the discrimination of the propensity score. The patients were then stratified into quartiles based on the propensity score. Overall survival (OS), the primary outcome measure of this study, was calculated using the Kaplan–Meier method and compared between the treatment groups by a log-rank test stratified according to the propensity score. We also performed a propensity score matching with a caliper of 20 % of the standard deviation of the propensity score and compared OS between the two groups. Age, ECOG-PS, white blood cell count, hemoglobin level, peripheral blood blast percentage, serum creatinine level, and serum total bilirubin level were evaluated as continuous variables. We did not use cytogenetic data to calculate the propensity score, since it generally takes at least 2 weeks to obtain cytogenetic data and we have to decide first-line treatment before obtaining cytogenetic data.

We confirmed the impact of intensive chemotherapy by a multivariate analysis using proportional hazard modeling to adjust for the other factors at diagnosis, which were selected in a stepwise manner based on the AIC. All statistical analyses

were performed with EZR (Saitama Medical Center, Jichi Medical University, http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6-3) designed to add statistical functions frequently used in biostatistics.

Results

Characteristics of the patients

The characteristics of the patients are shown in Table 1. There were 47 males and 34 females with a median age of 76 years (range; 70–97). Sixteen patients had poor chromosome abnormalities, including complex karyotype in 11. Twenty-seven patients had a prior history of MDS. The PS was 2 or more in 44 patients, including PS 2 in 11, PS 3 in 17, and PS 4 in 16. The most frequent comorbidity was hypertension in 28 patients (34.6 %), followed by ischemic heart disease in eight (9.9 %). The median number of comorbidities was 2 (range; 0–7). Infectious diseases such as pneumonia coexisted at diagnosis in 39 patients (48.1 %). An elevated serum total bilirubin of 1.5 mg/dl or higher was observed in four patients. None of the patients had elevated serum creatinine of 2.0 mg/dL or higher.

Table 1 Patient characteristics

Sex	
Male	47
Female	34
Age, median (range)	76 (70–97)
FAB classification	
AML M0	3
AML M1	21
AML M2	37
AML M4	8
AML M5	4
AML M6	4
AML M7	3
Unknown	1
Chromosomal abnormality	
Favorable	5
Intermediate	53
Poor	16
Unknown	7
WBC count, median (range)	5,200 (800–395,500)
Prior diagnosis of MDS	
Yes	27
No	54
Performance status	
0	14
1	23
2	11
3	17
4	16
Initial treatment	
No chemotherapy	7
Low-dose chemotherapy	29
Reduced-intensity chemotherapy	41
Standard chemotherapy	4

FAB French–American–British classification, *WBC* white blood cell, *AML* acute myelogenous leukemia, *MDS* myelodysplastic syndrome

Initial treatment of the patients and propensity score calculation

Seven, 29, 41, and four patients were classified into the no-chemotherapy, low-dose chemotherapy, reduced-intensity chemotherapy, and standard chemotherapy groups, respectively. The combination of behenoyl cytarabine and daunorubicin was exclusively used in the standard chemotherapy group, whereas such a combination was used in 14 of the 41 patients in the reduced-intensity chemotherapy group. Other regimens used in the reduced-intensity chemotherapy group included combinations of cytarabine and daunorubicin in 15, cytarabine and idarubicin in nine, and so on. The 36 patients in the former two groups and 45 patients in the latter two groups were classified into a non-intensive chemotherapy group and

Table 2 Factors evaluated in the logistic regression model

Deleted factors and the Akaike information criterion (AIC) values just before deletion

Factor	AIC
Infectious complications	102.62
Prior diagnosis of MDS	100.67
Serum creatinine level	98.87
Serum total bilirubin level	97.02
Hemoglobin level	95.15
White blood cell count	94.25
Cognitive function	93.64
Institutes	93.59

Final model (AIC=93.57)

Factor	Odds ratio (95 % confidence interval)	*P* value
Blast percent	1.04 (1.02–1.06)	0.00063
Performance status	0.71 (0.43–1.16)	0.17
Sex	0.42 (0.14–1.23)	0.11
Age	0.87 (0.78–0.97)	0.01

an intensive chemotherapy group, respectively. The factors that were used to calculate the propensity score were selected from the 12 factors at diagnosis based on the AIC and multicollinearity. Ultimately, age, sex, ECOG-PS, and peripheral blood blast cell percentage were used to calculate the propensity score (Table 2). The *C* statistic was 0.813, which indicates good discrimination. Patients were stratified into quartiles based on the propensity score. The numbers of patients in the first, second, third, and forth quartiles who received intensive chemotherapy were 5 of 21, 10 of 20, 12 of 20, and 18 of 20, respectively.

Induction therapy

Complete remission was achieved in ten and 18 patients in the non-intensive chemotherapy group and the intensive chemotherapy group, respectively (27.8 vs. 40 %, *P*=

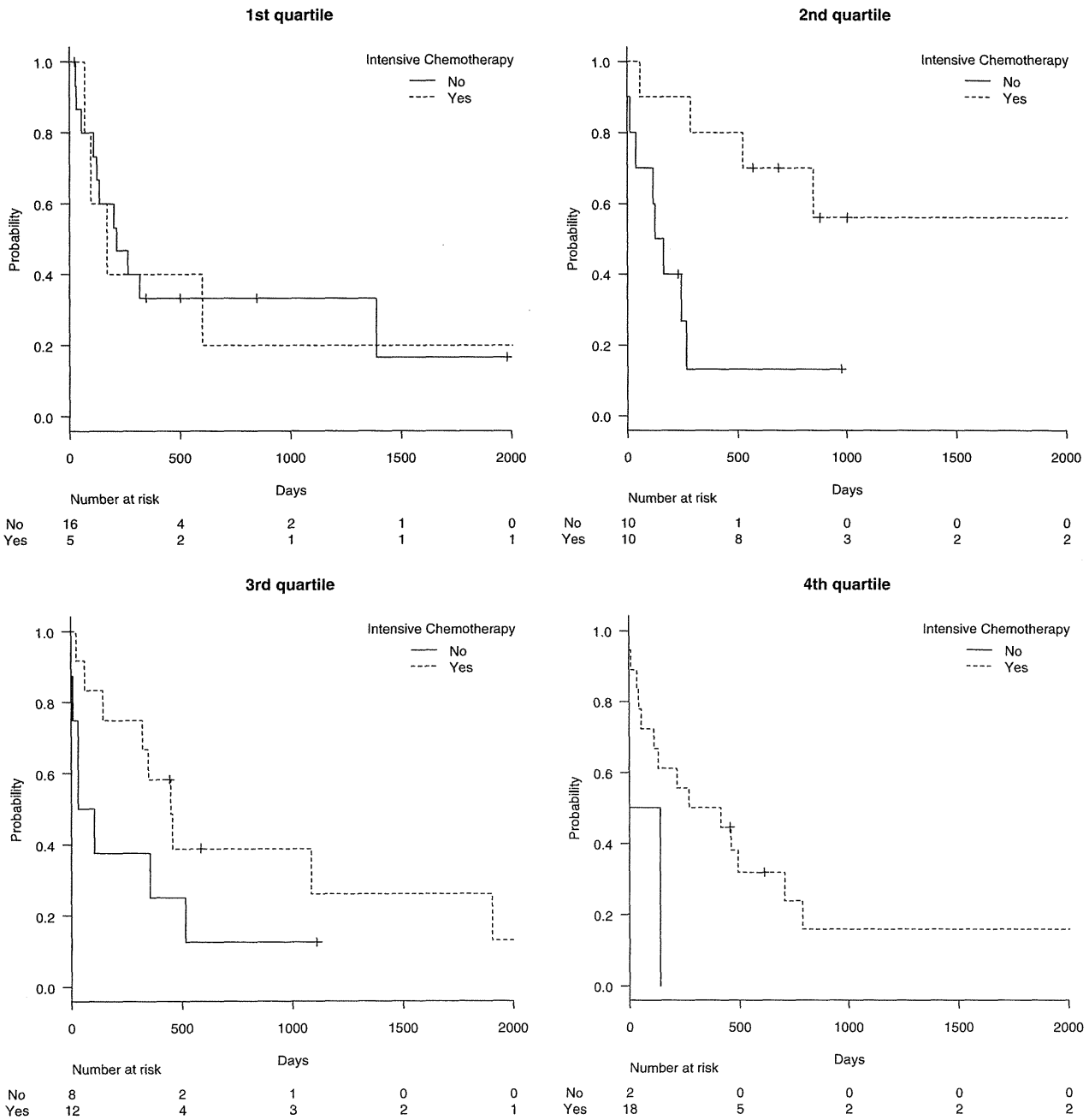

Fig. 1 Overall survival grouped according to the treatment intensity stratified according to the propensity score quartile

0.35). The major reason for remission induction failure was the insufficient suppression of leukemic cells. Death during myelosuppression was observed in three and two patients in the non-intensive chemotherapy group and the intensive chemotherapy group, respectively.

Overall survival

For all of the patients, overall survival was 43.5, 30.3, and 24.3 % at 1, 2, and 3 years, respectively. There was a statistically significant difference in overall survival between the non-intensive chemotherapy group and the intensive chemotherapy group (P=0.020). To adjust for a selection bias, we compared the two groups after stratification according to the propensity score. The overall P value by the stratified log-rank test was 0.0088, and the P value of each stratum was 0.91, 0.0068, 0.16, and 0.091 for the first, second, third, and forth propensity score quartiles, respectively (Fig. 1). Especially, in the combined second and third quartiles, in which the intensive and non-intensive strategies were chosen evenly, overall survival at 3 years was 37.5 % for the intensive chemotherapy group and 13.0 % for the non-intensive chemotherapy group (P=0.0022).

Next, we performed propensity score matching with a caliper of 20 % of the standard deviation of the propensity score and 22 patients in the intensive chemotherapy group were 1:1 matched to 22 patients in the non-intensive chemotherapy group. Among these patients, the use of intensive chemotherapy was shown to significantly improve survival (HR 0.25, 95 %CI 0.084–0.75, p=0.013, Fig. 2).

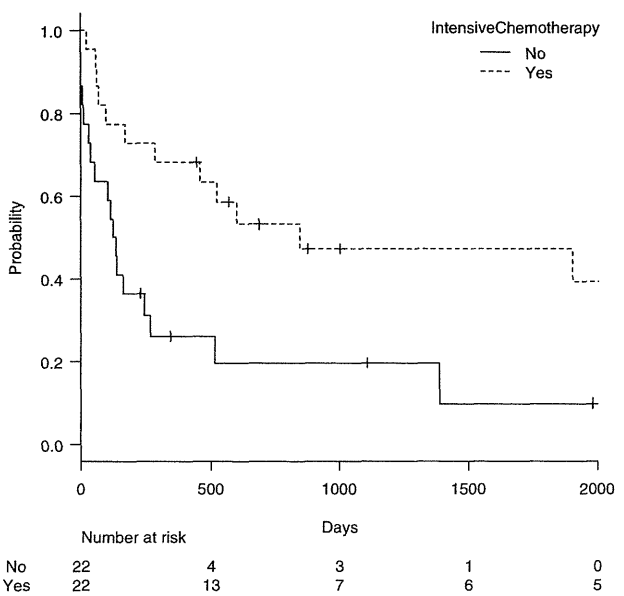

Fig. 2 Overall survival grouped according to the treatment intensity in propensity score matched-pair analysis

Finally, we performed proportional hazard regression modeling to confirm the superiority of intensive chemotherapy by adjusting for the other important factors at diagnosis, including a karyotype analysis. The factors that were used for adjustment, which were selected based on the AIC of proportional hazard modeling, included white blood cell count, total bilirubin level, cognitive function, and poor chromosome abnormality. Intensive chemotherapy as a first-line treatment was significantly associated with better survival after adjusting for these factors (hazard ratio 0.50, 95 % confidence interval 0.27–0.93, P=0.028).

The most frequent cause of death was the progression of AML in 29 patients, followed by infection in 17, and hemorrhage in eight (Table 3). There was no significant difference in the proportion of the causes of death between the non-intensive chemotherapy group and the intensive chemotherapy group (P=0.713).

Discussion

It is difficult to treat AML in the elderly. Complete remission must be achieved to confer long-term survival. On the other hand, strong remission induction chemotherapy is associated with a high treatment-related mortality rate in elderly patients. A clinical trial conducted by the European Organization for the Research and Treatment of Cancer (EORTC) randomized AML patients more than 65 years of age into intensive induction chemotherapy with daunorubicin, cytarabine, and vincristine versus observation until the time of disease progression followed by palliative therapy with hydroxyurea and subcutaneous cytarabine [16]. The induction chemotherapy group showed a significantly higher complete remission rate (58 vs. 0 %), and a longer median survival (21 vs. 11 weeks). However, patients with organ dysfunction or a poor performance status were excluded from the study, and, therefore, this study does not accurately reflect elderly patients with AML in daily clinical practice. Tilly et al. reported a contradicting result [17]. They randomized AML patients greater than the age of 65 years into induction chemotherapy including rubidazone and cytarabine or low-dose cytarabine treatment. Although the complete remission rate was higher with intensive therapy, there was no

Table 3 Cause of death grouped according to the treatment intensity

	Intensive chemotherapy	
	No	Yes
Leukemia	10	18
Infection	11	7
Hemorrhage	4	4
Heart failure	1	1
Other	3	2

survival advantage associated with intensive induction chemotherapy due to increased early mortality. Therefore, the optimal treatment for elderly patients with AML remains controversial.

In this study, we retrospectively analyzed the clinical outcome in AML patients aged at least 70 years. Although this study includes many limitations due to its retrospective nature, the subjects of this study consisted of elderly AML patients in real daily practice. In fact, more than half of the patients had a poor performance status (ECOG-PS 2–4). Forty-five of the 81 patients received intensive chemotherapy, whereas 36 did not. Of course, there must be a selection bias. For example, the patient age was significantly younger in the intensive chemotherapy group (75.7 vs. 78.9 years, $P=0.0090$). Therefore, we calculated a propensity score to adjust for the background characteristics at diagnosis. The propensity score calculated based on four factors at diagnosis showed good discrimination, with a C statistic of 0.813. Overall survival was shown to be significantly better in the intensive chemotherapy group by a stratified log-rank test. In addition, the survival advantage in the intensive chemotherapy group was clearly observed in the combined second and third quartiles. Intensive chemotherapy was performed in 10 of 20 and 12 of 20 patients in the second and third quartile patients, respectively, and therefore, the intensive and non-intensive strategies were chosen evenly. This fact may indicate that it can be difficult to decide whether or not intensive chemotherapy should be performed in these patients. The current data may suggest that intensive chemotherapy prolongs overall survival in such patients.

Recently, however, Kantarjian et al. reported that the prognosis of elderly patients with AML is poor even with intensive chemotherapy. The major difference between their study and ours is the proportion of patients with unfavorable karyotype (54 vs. 22 %). In fact, when we analyzed only in patients with unfavorable karyotype, two-year survival was 14.3 and 11.1 % with intensive and non-intensive chemotherapies, respectively. Therefore, the benefit of intensive chemotherapy might be limited in patients without unfavorable karyotype.

In this study, we could not assess the quality of life (QOL) of the patients. The length of the hospital stay is also an important point. The previous randomized trial by EORTC showed that there was no difference in the number of days spent in the hospital between the two treatment strategies. In contrast, in Tilly's study, the hospital stay in the low-dose cytarabine group was shorter than that in the intensive chemotherapy group. In addition, severe infectious complications were more frequent in the latter. Therefore, the effect of initial treatment intensity on the QOL of the elderly AML patients is still controversial.

In conclusion, intensive chemotherapy may be recommended for elderly patients with AML to prolong overall survival, as long as patients are considered to be able to tolerate such treatment. However, the impact of intensive chemotherapy on the QOL of the patients should be evaluated further.

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ORIGINAL ARTICLE

Allogeneic hematopoietic stem cell transplantation for patients with mildly reduced renal function as defined based on creatinine clearance before transplantation

Kumi Oshima · Yoshinobu Kanda · Yasuhito Nanya · Masatsugu Tanaka · Chiaki Nakaseko · Shingo Yano · Shin Fujisawa · Hiroyuki Fujita · Akira Yokota · Satoshi Takahashi · Heiwa Kanamori · Shinichiro Okamoto · for the Kanto Study Group for Cell Therapy (KSGCT)

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Abstract While renal comorbidity is generally defined by the serum creatinine level, the creatinine clearance rate (Ccr) is a more accurate indicator of renal function. Therefore, we retrospectively assessed how mildly reduced renal function as defined based on Ccr affects the outcome after allogeneic hematopoietic stem cell transplantation (HSCT). Patients who underwent allogeneic HSCT at the eight institutes of the Kanto Study Group for Cell Therapy were included in this study. Based on the corrected Ccr, patients were classified into group 0 (n=440, ≥90 mL/min/1.73 m^2), group 1 (n=56, 60–89 mL/min/1.73 m^2), or group 2 (n=11, 30–59 mL/min/1.73 m^2). Therefore, 67 patients were considered to have mild renal impairment, whereas only 2 had a serum creatinine level higher than 1.2 mg/dL. Twenty-eight patients required hemodialysis after HSCT, with 5.5, 5.4, and 9.1 % in groups 0, 1, and 2, respectively (p=0.65). The incidence of non-relapse mortality (NRM) was higher in group 2, although these differences were not statistically significant probably due to the small sample size (23.7, 28.2, and 47.2 % at 3 years, p=0.20). In conclusion, NRM may be associated with mildly reduced renal function before allogeneic HSCT, which cannot be detected by measurement of the serum creatinine level alone.

Keywords HSCT · Reduced renal function · Chronic kidney disease

K. Oshima · Y. Kanda (✉)
Division of Hematology, Saitama Medical Center,
Jichi Medical University,
1-847, Amanuma-cho, Omiya-ku,
Saitama-shi, Saitama 330-8503, Japan
e-mail: ycanda-tky@umin.ac.jp

Y. Nanya
Department of Hematology and Oncology, University of Tokyo,
Tokyo, Japan

M. Tanaka · H. Kanamori
Department of Hematology, Kanagawa Cancer Center,
Yokohama, Kanagawa, Japan

C. Nakaseko
Department of Hematology, School of Medicine, Chiba University,
Chiba, Japan

S. Yano
Division of Clinical Oncology and Hematology, Department of Internal Medicine, Jikei University School of Medicine,
Tokyo, Japan

S. Fujisawa
Department of Hematology, Yokohama City University Medical Center,
Yokohama, Kanagawa, Japan

H. Fujita
Department of Rheumatology/Hematology/Infectious Disease,
Yokohama City University Hospital,
Yokohama, Kanagawa, Japan

A. Yokota
Department of Internal Medicine, Chiba Aoba Municipal Hospital,
Chiba, Japan

S. Takahashi
Division of Molecular Therapy, Advanced Clinical Research Center, Institute of Medical Science, University of Tokyo,
Tokyo, Japan

S. Okamoto
Division of Hematology, Department of Medicine,
Keio University School of Medicine,
Tokyo, Japan

Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for patients with various hematological diseases, but it is associated with a high rate of treatment-related toxicities. In addition, comorbidities before HSCT significantly affect outcome of HSCT. Reduced renal function is one of the risk factors for transplant-related toxicities, and patients with significant renal dysfunction have traditionally been excluded from HSCT because of unacceptably high transplant-related mortality (TRM) [1]. In fact, renal dysfunction before HSCT is included as a risk factor in the hematopoietic cell transplantation comorbidity index (HCT-CI) [2, 3], which predicts TRM and survival after HSCT. In the HCT-CI, as well as in other studies, renal function was estimated using the serum creatinine level before HSCT. However, the serum creatinine level is affected not only by renal function but also by the patient's age, sex, and muscle volume. While the effect of age and sex can be adjusted by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, individual variations in muscle volume cannot.

The creatinine clearance rate (Ccr) is the volume of blood plasma that is cleared of creatinine per unit time and is a useful and exact measure for approximating the glomerular filtration rate (GFR). Ccr has an important role in estimating the renal function and is used in the criteria for chronic kidney disease (CKD) [4, 5]. However, the impact of renal function as evaluated using Ccr instead of the serum creatinine level before HSCT on the clinical outcome has not yet been investigated. Therefore, the aim of this study was to assess the outcome of patients with mildly reduced renal function as defined by Ccr before allogeneic HSCT.

Patients and methods

Study population

The study population consisted of patients who underwent allogeneic HSCT using a calcineurin inhibitor between January 2004 and December 2008 at the eight institutes of the Kanto Study Group for Cell Therapy (KSGCT). Patients with available Ccr data before HSCT were included in this study. This study was approved by the Institutional Review Board of each institute.

Data collection

The patients' data were extracted from the database of KSGCT, except for Ccr, which is not included in the database. Therefore, Ccr data were collected from each institute using a survey sheet. Ccr was calculated from a serum sample and 24-h urine sample, and corrected by the actual body surface area using the following formula:

$$\mathrm{Ccr}(\mathrm{mL/min/1.73\,m^2}) = \left(\mathrm{Ucr\,(mg/dL)} \times \mathrm{UV(mL/day)} \times 1.73(\mathrm{m^2})\right) / \left(\mathrm{Scr\,(mg/dL)} \times \mathrm{BSA\ (m^2)} \times 1{,}440(\mathrm{min/day})\right)$$

(Scr, serum creatinine (in milligrams per deciliter); Ucr, creatinine of 24-h urine sample (in milligrams per deciliter); UV, urine volume (in milliliters per day); and BSA, actual body surface area (in square meters).

In patients in whom the Ccr was measured more than once before HSCT, the average values were used in this study. We considered that the urine collection was performed accurately, as the mean creatinine excretion in urine was 1,382 mg/day (standard deviation [SD], 440 mg/day) in male patients and 1,141 mg/day (SD, 476 mg/day) in female patients. The serum creatinine level was measured using the enzymatic creatinine assay in all centers with the same normal ranges.

We also evaluated Ccr using the CKD-EPI formula as follows [6]:

$$\mathrm{GFR} = 141 \times \min(\mathrm{Scr}/\kappa, 1)^{\alpha} \times \max(\mathrm{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{age}} \times 1.018\ [\text{if female}] \times 1.159[\text{if African American}]$$

(Scr, serum creatinine (in milligrams per deciliter); κ, 0.7 for females and 0.9 for males; and α, −0.329 for females and −0.411 for males; min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1).

Statistical considerations

Overall survival was calculated using the Kaplan–Meier method and compared among groups by the log-rank test. Non-relapse mortality was calculated by treating relapse as a competing risk and compared among groups using Gray's method [7]. Non-relapse mortality was adjusted for other confounding factors using the Fine and Gray proportional hazard regression [8]. The p values of less than 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University)

[9], which is a graphical user interface for R (the R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6-3) that includes statistical functions that are frequently used in biostatistics.

Results

Characteristics of the patients

Five hundred seven patients were included in this study. There were 285 males and 222 females with a median age of 44 (range, 15–68 years). All patients had underlying hematological malignancies, except for 14 patients with aplastic anemia. The median serum creatinine level before conditioning was 0.65 (range, 0.32–1.33 mg/dL). Only two patients had a serum creatinine level between 1.2 and 2.0 mg/dL, which corresponds to mild renal impairment in HCT-CI, and none of the patients showed a serum creatinine level higher than 2.0 mg/dL. On the other hand, 440 patients had normal renal function (group 0, Ccr at 90 mL/min/1.73 m^2 or higher), and the other 67 patients had mildly reduced renal function (<90 mL/min/1.73 m^2). The latter 67 patients were further classified into group 1 (56 patients, 11.0 %) and group 2 (11 patients, 2.2 %), according to corrected Ccr values of 60–89 and 30–59 mL/min/1.73 m^2, respectively.

Patient characteristics grouped according to the corrected Ccr are shown in Table 1. Of the two patients with a serum creatinine level higher than 1.2 mg/dL, one patient, a 55-year-old male, was in group 0 (serum creatinine, 1.33 mg/dL, and Ccr, 94.7 mL/min/1.73 m^2), and the other, a 50-year-old male, was in group 2 (serum creatinine, 1.24 mg/dL, and Ccr, 39.7 mL/min/1.73 m^2). Based on the CKD-EPI equation, the GFRs of these patients were estimated to be 59.8 and 67.3 mL/min/1.73 m^2, respectively. These findings suggested that it is important to measure Ccr exactly to accurately assess renal function before HSCT.

Treatment outcome

Engraftment was achieved in 92.5, 92.5, and 100 % of the patients in groups 0, 1, and 2, respectively (p=0.67). Grade II to IV acute graft-versus-host disease (GVHD) was observed in 34.8, 32.1, and 45.5 % of the patients in groups 0, 1, and 2, respectively (p=0.70). Figure 1 shows the overall survival after HSCT. There was no significant difference in overall survival among the three groups (51.5, 41.8, and 43.6 % at 3 years, p=0.18). On the other hand, the incidence of non-relapse mortality was higher in group 2 although the differences were not statistically significant (23.7, 28.2, and 47.2 at 3 years, p=0.20, Fig. 2). Next, the impact of renal function on the incidence of non-relapse mortality was adjusted for patient age, which was the only significant factor for non-relapse mortality by a multivariate analysis. The adjusted hazard ratios were 1.18 (95 % CI 0.65–2.14, p=0.59) for group 1 and 1.98 (95 % CI 0.81–4.82, p=0.13) for group 2 (Table 2).

Hemodialysis after transplantation

Overall, 28 patients required hemodialysis for severe renal failure after HSCT. Hemodialysis was initiated within 100 days after HSCT in 20 patients and after 100 days in 8 patients. The probability of requiring hemodialysis was 9.1 % (n=1) in group 2, which was higher than those in groups 1 (n=3, 5.4 %) and 0 (n=24, 5.5 %), but the differences were not statistically significant (p=0.65). Hemodialysis was discontinued in only six patients in group 0. Of the other 22 patients, only 3 patients (two in group 0 and one in group 1) were alive at the last follow-up, and the remaining 19 patients have died, mainly (n=15) without relapse of the underlying disease.

Discussion

The Charlson Comorbidity Index (CCI) is a classical measure of the impact of different comorbidities on the index disease [10]. In the CCI, mild renal comorbidity is defined as serum creatinine of 2–3 mg/dL, and moderate–severe renal comorbidity is defined as serum creatinine>3 mg/dL, renal dialysis, or renal transplant. These definitions were modified in the HCT-CI, because such comorbidities in the CCI are rarely encountered in HSCT patients [3]. In the HCT-CI, mild renal comorbidity is defined as serum creatinine of 1.2–2.0 mg/dL, and moderate to severe renal comorbidity is defined as serum creatinine >2 mg/dL, renal dialysis, or renal transplant [3]. In the analysis of HCT-CI, mild renal comorbidity did not correlate with non-relapse mortality (multivariate hazard ratio, 0.8), whereas moderate to severe renal comorbidity was associated with a significantly higher non-relapse mortality (multivariate hazard ratio, 2.6) [3]. However, in the current study, only two patients (0.4 %) met the criteria of mild renal comorbidity, and none met the criteria of moderate to severe renal comorbidity in the HCT-CI.

The serum creatinine level is not sensitive enough to detect mildly reduced renal function since it does not increase until the GFR is reduced by approximately half. In addition, the renal function estimated from the serum creatinine level is lower than the actual renal function in patients with decreased muscle volume. This could be a major problem in heavily pretreated HSCT recipients. Therefore, in this study, we used Ccr as a

Table 1 Patient characteristics

		Normal (n=440)	Group 1 (n=56)	Group 2 (n=11)
Age		43 (15–68)	50 (17–64)	52 (21–67)
Sex	Male	256	26	3
	Female	184	30	8
Serum creatinine		0.63 (0.32–1.33)	0.74 (0.44–1.11)	0.74 (0.43–1.24)
Serum creatinine group	0–1.2 mg/dL	439	56	10
	1.2–2.0 mg/dL	1	0	1
	2.0–mg/dL	0	0	0
Corrected creatinine clearance		139 (90–347)	78 (61–89)	46 (32–57)
CKD-EPI estimation		116 (60–168)	103 (62–147)	92 (56–132)
Disease	AML	207	19	4
	ALL	85	14	3
	CML	21	2	0
	MDS/MPN	62	4	2
	Lymphoma	32	12	2
	AA	11	3	0
	Others	22	2	0
Donor	Related	196	23	3
	Unrelated	236	33	8
Stem cell source	BM	269	29	7
	BM + PB	0	1	0
	PB	100	14	1
	CB	71	12	3

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, *AML* acute myelogeneous leukemia, *ALL* acute lymphoid leukemia, *CML* chronic myelogeneous leukemia, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasms, *AA* aplastic anemia, *BM* bone marrow, *PB* peripheral blood stem cell, *CB* cord blood

more accurate estimator of renal function. In this cohort, 2.2 % of the patients had a corrected Ccr level less than 60 mL/min/1.73 m^2, which meets the criteria of CKD stage 3, and 11 % of the patients had a corrected Ccr between 60 and 89 mL/min/1.73 m^2, which meets the criteria of CKD stage 2, whereas only two patients (0.4 %) had a serum creatinine level higher than 1.2 mg/dL. Therefore, mild renal comorbidity, as assessed by the serum creatinine level, was not sensitive enough to detect mild renal impairment. The use of serum cystatin C level to estimate GFR can be an alternative approach [11]. The cystatin C level is not affected by the muscle volume, and the estimation of GFR with cystatin C does not require urine collection. However, the cystatin C level has been correlated with markers of inflammation such as C-reactive protein, body size, and diabetes [12, 13]. Therefore, we did not use cystatin C to estimate GFR in our cohort.

In this study, the incidence of non-relapse mortality was higher in patients with a Ccr level less than 60 mL/min/1.73 m^2. While this difference was not statistically significant, the analysis was underpowered due to the small sample size. The renal impairment before HSCT may affect the transplantation outcome in several ways. First, additional renal damage caused by the conditioning regimen, calcineurin inhibitors, and antimicrobial agents may lead to severe renal insufficiency requiring hemodialysis. In addition, the dose of calcineurin inhibitors is often reduced to avoid renal toxicity, which may increase the incidence of acute GVHD. Furthermore, the use of steroid instead of calcineurin inhibitors may increase the risk of infectious complications. In this study, there was no apparent difference in the incidences of hemodialysis and acute GVHD, and therefore, the increase in the incidence of non-relapse mortality in patients with mild renal impairment was multifactorial.

With regard to the impact of renal impairment before HSCT on the incidence of acute renal failure after HSCT, there have been conflicting reports [14]. Zager

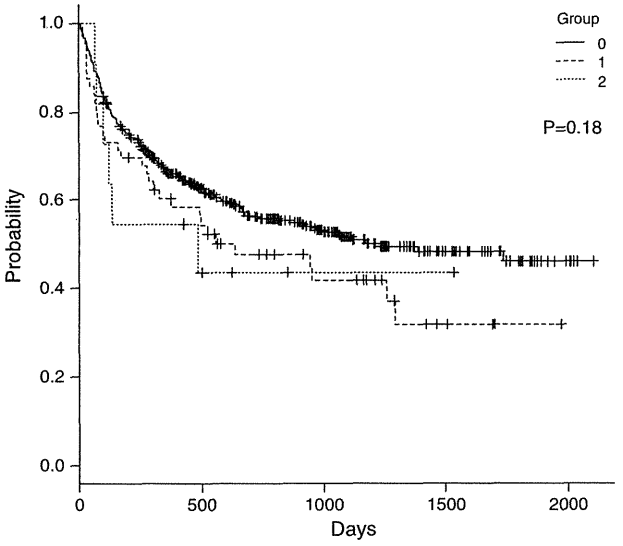

Fig. 1 Overall survival grouped according to renal function before transplantation. Group 0: normal renal function; group 1: corrected creatinine clearance, 60–89 mL/min/1.73 m^2; group 2: corrected creatinine clearance, 30–59 mL/min/1.73 m^2

et al. reported that the higher serum creatinine level before HSCT was independently associated with the subsequent development of acute renal failure requiring hemodialysis [15]. However, a subsequent report from the same institution showed that the increase in baseline

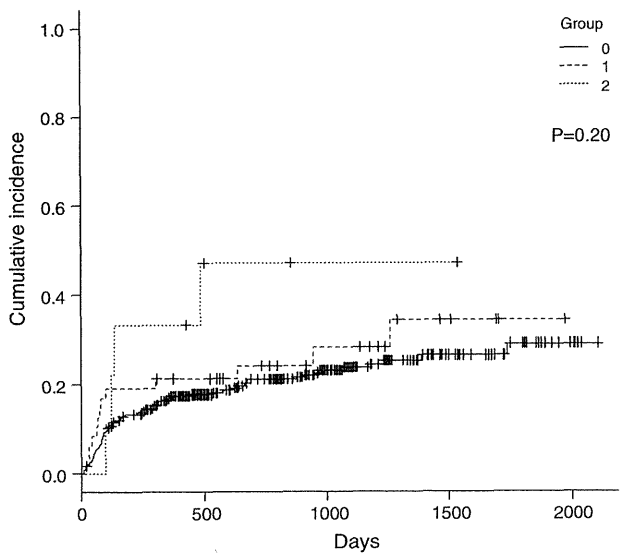

Fig. 2 Incidence of non-relapse mortality grouped according to renal function before transplantation. Group 0: normal renal function; group 1: corrected creatinine clearance, 60–89 mL/min/1.73 m^2; group 2: corrected creatinine clearance, 30–59 mL/min/1.73 m^2

Table 2 Multivariate analysis for the incidence of non-relapse mortality

		Hazard ratio	*p* value
Age		1.02 (1.01–1.04)	0.0067
Corrected Ccr group	0	1	
	1	1.18 (0.65–2.14)	0.59
	2	1.98 (0.81–4.82)	0.13

serum creatinine level was associated with a decrease in the incidence of acute renal failure after HSCT [16]. The latter finding might be affected by the definition of acute renal failure. They defined acute renal failure as a doubling of baseline serum creatinine level, and therefore, patients with a low baseline level required a smaller absolute change to meet the criterion. However, they also suggested a possibility based on the experimental animal data that the induction of nephrotoxic injury may confer protection against subsequent renal damage [17, 18]. In fact, Zager showed that both the frequency and degree of reduction in estimated GFR after HSCT were lower in patients with lower estimated GFR before HSCT [19]. However, these data should be interpreted with caution, as they analyzed only patients who were alive at 1 year after HSCT, and therefore, patients who died early after HSCT were excluded from the analysis. In addition, as the author commented in the paper, the limitation of the analysis was the use of estimated GFR based on the Modification of Diet in Renal Disease equation.

The use of reduced-intensity conditioning may positively affect the transplantation outcome in patients with renal impairment. In fact, Kersting et al. reported that patients with mildly reduced renal function can be safely treated in non-myeloablative HSCT [20]. The current study did not include enough patients to evaluate the impact of the conditioning regimen on the relationship between renal function and the incidence of non-relapse mortality. However, we did not find a tendency for a smaller effect of renal impairment in patients who received reduced-intensity conditioning (data not shown).

In conclusion, mildly reduced renal function before allogeneic HSCT may increase the incidence of non-relapse mortality. Calculation of Ccr using a serum sample and 24-h urine sample is required to detect mild renal impairment. However, further studies will be required to identify a strategy to reduce non-relapse mortality in patients with mild renal impairment.

Conflict of interest The authors declare that they have no conflict of interest.

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Short communication

Pharmacokinetics of micafungin in patients undergoing allogeneic hematopoietic stem cell transplantation

K. Oshima, Y. Kanda, S. Kako, K. Ohno, S. Kishino, M. Kurokawa. Pharmacokinetics of micafungin in patients undergoing allogeneic hematopoietic stem cell transplantation.
Transpl Infect Dis 2013: **15**: 323–327. All rights reserved

Abstract: *Objectives.* Micafungin (MCFG) is an antifungal agent that is widely used for the treatment of invasive fungal infection. Although the pharmacokinetics of MCFG is considered to depend on the hepatic metabolism, the impact of hepatic function on the pharmacokinetics of MCFG has been inconsistent among previous studies. The object of this study was to evaluate the relationship between plasma MCFG concentration and clinical and laboratory data.
Patients and methods. We examined the plasma concentration of MCFG in 10 patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT). MCFG at 150 mg/day was administered intravenously a median of 58.5 days after HSCT. Trough and peak concentrations of MCFG (Cmin and Cmax) were measured at a median of 5.5 days after the first administration of MCFG.
Results. The presence of graft-versus-host disease involving the liver at blood sampling was associated with significantly higher Cmin and Cmax of MCFG. Among the laboratory data, Cmin and Cmax were significantly higher in patients with severely impaired hepatic function defined as serum total bilirubin (TBi) level >5 mg/dL and/or serum gamma-glutamyltransferase (γ-GTP) level >500 IU/L, but the presence of mildly impaired hepatic function defined as serum TBi level >2 mg/dL and/or serum γ-GTP level >200 IU/L did not affect Cmin and Cmax. Renal function did not show significant impact on Cmin and Cmax.
Conclusion. These findings suggest that the pharmacokinetics of MCFG is affected only by severely impaired liver function.

K. Oshima[1,2], Y. Kanda[1,2], S. Kako[1,2], K. Ohno[3], S. Kishino[3], M. Kurokawa[2,4]

[1]Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan, [2]Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, [3]Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University, Tokyo, Japan, [4]Department of Cell Therapy and Transplantation Medicine, University of Tokyo Hospital, Tokyo, Japan

Key words: pharmacokinetics; micafungin; liver function; HSCT

Correspondence to:
Mineo Kurokawa, MD, PhD, Department of Hematology & Oncology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Tel: +81 3 5800 9092
Fax: +81 3 5840 8667
E-mail: kurokawa-tky@umin.ac.jp

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Micafungin (MCFG) is classified as an echinocandin antifungal agent that specifically inhibits the synthesis of (1,3)-β-D-glucan, a key component of fungal cell walls to retain the rigidity to resist osmotic pressure, and has been found to have potent antifungal activity against a broad spectrum of *Candida* and *Aspergillus* species (1, 2). MCFG exhibits linear pharmacokinetics after intravenous (IV) administration. It distributes well into tissues including lung, liver, and spleen, except for the central nervous system. Following initial distribution, MCFG is taken up by transporter-mediated mechanisms and degraded slowly primarily in the liver by catechol-O-methyltransferase pathway (3). Its metabolites are inactive, except that 2 minor metabolites exhibit antifungal activities. MCFG is a poor substrate for cytochrome P450 enzymes and does not inhibit them. MCFG is predominantly cleared by hepatocyte uptake and biliary excretion, and therefore, MCFG is eliminated mainly by feces and <15% by urine (1, 4).

Although the pharmacokinetics of MCFG is considered to highly depend on the hepatic metabolism, the impact of impaired hepatic function on the pharmacokinetics of MCFG has been inconsistent among previous studies. Therefore, in this study, we examined the plasma concentration of MCFG in patients who