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Prognosis of acute myeloid leukemia transformed from myelodysplastic syndromes: A multicenter retrospective study

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ABSTRACT

Myelodysplastic syndromes (MDS) often transform into acute leukemia (AL-MDS), although its prognostic details have not been examined thoroughly. We retrospectively analyzed the prognosis of 189 AL-MDS patients. Ninety-four patients received best supportive care (BSC), and 94 patients received disease-modifying therapies (DMT) that included chemotherapy (CHT) for 65 patients, allogeneic stem-cell transplantation (allo-SCT) for 21 patients, and other therapies for 8 patients. The median survival time was 142 days. In patients treated with BSC, platelet count alone was an independent prognostic factor. In younger patients treated with DMT (<60 years, $N = 25$), allo-SCT was an independent prognostic factor associated with longer survival. In older patients treated with DMT (≥60 years, $N = 69$), the therapy type did not affect survival, and performance status and MDS-specific comorbidity index were independent prognostic factors.

1. Introduction

Myelodysplastic syndromes (MDS) are hematopoietic neoplasia with heterogeneous biology, such as a variety of genetic backgrounds and of disease progression mechanisms [1]. A majority of MDS patients are over 60 years of age, with median onset at around 70 years [2,3]. MDS often transform into the acute leukemia phase (acute leukemia from MDS [AL-MDS]), which is indistinguishable from de novo acute myeloid leukemia (AML) by conventional laboratory tests. The prognosis of AL-MDS patients is generally poor [4], but its details, such as prognostic factors, appropriate treatment, and median survival time, have not been examined thoroughly. Most previous studies treated a small number of AL-MDS patients whose data were often combined with data from de novo AML patients and from acute leukemia patients who were transformed from other hematological diseases with different biology, such as myeloproliferative neoplasia and aplastic anemia [5,6]. Among the recent literature, Rizzieri et al. [7] reported the results of conventional-dose chemotherapy (CHT) for AML patients including 45 AL-MDS patients. Morita et al. [8] compared the results of conventional-dose and low-dose CHT for patients with myeloid leukemia including 54 AL-MDS patients. Bello et al. [9] treated 61 patients, most of whom were AL-MDS, with conventional-dose CHT. Overall, CHT for AL-MDS was not notably beneficial, and only a tiny fraction of patients achieved long-term remission.

Prognostic information for AL-MDS is particularly important when considering that most AL-MDS patients are elderly and thus are at greater risk when receiving toxic therapies and that various targeted therapies for MDS and AML are under clinical trials and at the preclinical stage [10,11]. Since the biology of MDS is different from that of de novo AML, the prognostic factors utilized for de novo AML are probably inappropriate for AL-MDS patients. Meanwhile, prognostic scoring systems for predicting the overall survival of MDS patients have been introduced in clinical practice [12,13], although their validity for AL-MDS patients has not yet been examined.

In this multicenter retrospective study, we analyzed the prognosis of 189 patients with AL-MDS who were treated at institutions

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Table 1
Patient characteristics at MDS stage.

	All patients (n = 189)	Japan (n = 58)	Hungary (n = 38)	Netherlands (n = 40)	Austria (n = 53)
Median age, years	68 (range, 34–87)	68	71	65	69
Male/female	112/77	48/10	14/24	22/18	28/25
De novo MDS/secondary MDS	163/26	44/14	33/5	35/5	51/2
Diagnosis					
RCUD	29 (15.3)	6 (10.3)	8 (21)	3 (7.5)	12 (22.6)
RARS	5 (2.6)	0 (0)	2 (3.2)	3 (3)	0
RCMD	45 (23.8)	18 (31)	2 (3.2)	22 (55)	3 (5.7)
RAEB[a]	101 (53.4)	31 (53.4)	20 (52.6)	12 (30)	38 (65.5)
5q-syndrome	1 (0.5)	0 (0)	1 (2.6)	0	0
MDS-U	8 (5.3)	3 (5.1)	5 (13.1)	0	0
Cytogenetic category[b]					
Good	89 (47.0)	21 (36.2)	19 (50)	27 (67.5)	22 (41.3)
Intermediate	26 (13.8)	9 (15.5)	1 (2.6)	7 (17.5)	9 (17.0)
Poor	46 (24.3)	25 (43.1)	3 (7.9)	3 (7.5)	15 (28.3)
Unknown	28 (14.8)	3 (5.2)	15 (39.4)	3 (7.5)	7 (13.2)
IPSS					
Low	13 (6.9)	4 (6.9)	1 (2.6)	4 (10)	4 (7.5)
Intermediate-1	75 (39.7)	20 (34.4)	12 (31.5)	24 (60)	19 (35.8)
Intermediate-2	51 (27.0)	19 (32.8)	8 (25.8)	7 (17.5)	17 (32.0)
High	28 (14.8)	11 (19.0)	3 (7.9)	2 (5)	12 (22.6)
Unknown	22 (11.6)	4 (6.9)	14 (36.8)	3 (7.5)	1 (1.9)
WPSS					
Very low	15 (7.9)	6 (10.3)	3 (7.9)	4 (10)	2 (3.8)
Low	25 (13.2)	7 (12.0)	3 (7.9)	13 (32.5)	2 (3.8)
Intermediate	24 (12.7)	7 (12.0)	3 (7.9)	7 (17.5)	7 (13.2)
High	67 (35.4)	24 (41.0)	12 (31.6)	12 (30)	19 (35.8)
Very high	23 (12.1)	9 (15.5)	3 (7.9)	1 (2.5)	10 (18.9)
Unknown	35 (18.5)	5 (8.6)	14 (36.8)	3 (7.5)	13 (24.5)
Therapy at MDS stage					
BSC/SCT/CHT/unknown	91/17/62/19	33/13/5/7	35/0/2/1	23/3/3/11	0/1/52/0
Median time to AL-MDS, days	274 (range,16–4583)	270	151	256	388

RCUD, refractory cytopenia with unilineage dysplasia; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; SCT, allo-SCT. Data are number of patients and percentages in parentheses, unless otherwise stated.

[a] RAEB-1 and RAEB-2.

[b] Categories used in IPSS and WPSS.

experienced in the care of MDS patients. To the best of our knowledge, this is the largest study focusing on the prognosis of AL-MDS patients.

2. Patients and methods

2.1. Patients

Clinical data on consecutive AML patients, in whom a history of preceding MDS was confirmed and who were treated between 2000 and 2011, were obtained from five institutions in Japan (Nippon Medical School and Gunma University School of Medicine), Hungary (Semmelweis University), the Netherlands (VU University Medical Center), and Austria (Medical University of Vienna). Patients whose diagnoses of MDS were made according to the French–American–British classification [14] and the 2001 version of the World Health Organization (WHO) classification [15] were reclassified according to the latest WHO classification [16]. Patients whose diagnosis at the MDS stage was chronic myelomonocytic leukemia were excluded, while patients whose MDS developed after chemotherapy or radiation therapy for other diseases (secondary MDS) were included in this study. Cytogenetic analyses were performed using standard G-banding with trypsin-Giemsa staining. Karyotypes were interpreted using the International System for Cytogenetic Nomenclature criteria [17]. The International Prognostic Scoring System (IPSS) and WHO classification-based Prognostic Scoring System (WPSS) were applied to patients following previously reported methods [12,13]. AML transformation was diagnosed by the presence of 20% or more blasts in the peripheral blood or bone marrow (BM) [18]. The Charlson comorbidity index and MDS-specific comorbidity index (MDS-CI) were determined according to previous reports [4,19]. Therapy categories were defined as follows: (1) best supportive care (BSC) including hydroxyurea treatment for controlling leukocytosis; and (2) disease-modifying therapies (DMT) including conventional-dose CHT for AML, low-dose CHT, allogeneic stem-cell transplantation (allo-SCT), and other therapies. We searched the records for patients who received BSC for more than 6 months and then received CHT or allo-SCT and found only one such case. This patient, who received CHT after 13 months of BSC, was included in the BSC group and the survival data were censored at the time of CHT.

The present study was approved by the local Ethics Committees and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

2.2. Statistical analysis

Univariate survival analysis as a function of clinical variables was performed using the Kaplan–Meier method combined with the log-rank test. The variables included parameters at MDS stage and at AML transformation, and type of therapy received. Multivariate analysis of survival was performed using Cox proportional-hazard regression analysis. Variables with $p < 0.10$ in univariate analysis were included in the multivariate analysis. Data on survival time were censored at the last follow-up date when patients were alive. Analyses were performed using JMP 9.0 software (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics at MDS stage and association with time to AML transformation

The data from roughly similar numbers of patients were obtained from each country, which totaled 189 patients. The main patient characteristics are listed in Table 1. There were 112 men and 77 women with a median age of 68 years. The median time from the initial diagnosis to AML transformation was 274 days (range 16–4583; the patient with the longest time to transformation was a case with refractory cytopenia with multilineage dysplasia).

The proportion of high-risk patients as defined by the IPSS or WPSS was higher in our cohort compared with general MDS cohorts, because all our patients transformed to AML. Even in this selected population, cytogenetic category, IPSS, and WPSS were significantly associated with time to AML transformation (Table 2).

3.2. Patient characteristics at AML transformation and survival after AML

Patient characteristics at AML transformation, therapy received after AML, and median survival time from AML transformation are