Clinical Features and Outcomes of 666 Cases with Therapy-Related Myelodysplastic Syndrome (t-MDS)

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Abstract Therapy-related myelodysplastic syndrome (t-MDS) is a serious complication of chemoradiotherapy for primary diseases. This cohort was aimed to determine the clinical features and outcomes of t-MDS in comparison with de novo MDS. I retrieved data of 666 cases with t-MDS, and 29,703 cases with de novo MDS diagnosed between 2001 and 2012 from the database of U.S. National Cancer Institute. Survival curves were estimated, and Cox proportional hazards model was constructed. Compared with patients with de novo MDS, patients with t-MDS tended to be young (median age; 65 vs. 76 years, $p < 0.001$), and were more likely to be female-sex (51.4 vs. 44.7%, $p = 0.001$). Median overall survival (OS) and 5-year OS rate are significantly poorer in t-MDS than de novo MDS (17.2 months and 22% vs. 31 months and 32%, respectively, $p < .001$). In t-MDS cases, with a median follow-up of 16 months (range 1–143 months), 521 cases (78.2%) had died. Of which, 78 (15%) cases had died from acute myeloid leukemia, and 66 (12.7%) cases had died from solid cancers. Of the total 66 cases died from solid cancers; 19 cases (28.8%) died from cancer of lung/bronchus, 11 cases (16.7%) breast cancers, and 10 cases (15.2%) ovarian cancer. In a multivariate analysis adjusted for clinical features, calendar period and radiotherapy, the hazard of mortality was significantly low in de novo MDS

compared with t-MDS (hazard ratio 0.59; $p < .001$). In conclusions, t-MDS is a distinct entity of MDS in terms of clinical characteristics and prognosis.

Keywords Therapy-related · Secondary · De novo · Myelodysplastic syndrome · Survival · Prognosis

Introduction

Therapy-related myelodysplastic syndrome/acute myeloid leukemia (t-MDS/AML) is a serious complication of cytotoxic chemotherapy and/or radiation for a neoplastic or non-neoplastic diseases [1]. The incidence of t-MDS/AML following conventional therapy ranges from 0.8 to 6.3% at 20 years, and 1.1 to 24.3% at 5 years after autologous hematopoietic stem cell transplantation (HSCT) [2]. The classic form of t-MDS/AML follows treatment with alkylating agents and/or radiotherapy with latency period of 5–7 years. It is characterized by abnormalities of chromosomes 5 or 7 and preceded by a myelodysplastic phase. Less common form of t-MDS/AML occurring after exposure to topoisomerase II inhibitors with a short latency period (2–3 years), and it is characterized by balanced translocations involving 11q23 or 21q22 [1]. The most common primary cancers in t-MDS/AML are lymphomas and breast cancer, as these cancers are associated with prolonged survival [3, 4]. Patients with t-MDS/AML had unfavourable cytogenetics with a dismal prognosis (median survival was less than 1 year) [3, 4]. Five year survival of t-MDS/AML after allogeneic HSCT of 22% [5]. The patient age, cytogenetics, and complete remission at the time of transplantation are prognostic factors for survival of t-MDS/AML after allogeneic HSCT [6].

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This population-based cohort highlights, the clinical features, and survival outcomes of t-MDS in comparison with de novo MDS. To the best of my knowledge, it is the largest population-review of t-MDS to date.

Patients and Methods

SEER stands for Surveillance, Epidemiology, and End Results that currently collects and publishes cancer incidence and survival data from 18 population-based cancer registries covering approximately 28% of the US population. From 18 SEER registries [7], I extracted data of 44,878 cases with MDS between the years 2001 and 2012, which were identified by *International Classification of Diseases for Oncology Third Edition* (ICD-O-3) codes (9980–9989). Of 44,878 cases, sequential exclusions (Fig. 1) were then made for: diagnosed by autopsy/death certificate; unknown age of diagnosis; and those with unknown survival time or died at time of diagnosis. Patients with MDS with deletion of the long arm of chromosome 5 (del(5q)) [ICD-O-3: 9986] are also excluded from analysis, as they have a distinct clinical,

morphological and prognostic features [8]. The final cohort was 666 cases with t-MDS (ICD-O-3: 9987), and 29,703 cases with de novo MDS (ICD-O-3: 9980–9985, 9988, 9989) (Fig. 1). De novo MDS is identified as a first primary cancer in the SEER database. The SEER database includes variable determine cause of death (COD) “Cause of death to SEER site recode”. However, SEER database did not capture data regarding type of prior therapy, white cell count, serum lactate dehydrogenase, performance status, co-morbidities, subtypes of t-MDS, and cytogenetics.

Clinical and demographic features of patients were expressed as proportions (%) and frequencies (n) for categorical variables, or as median and range for continuous variables. Associations between categorical variables were analyzed using χ^2 analysis.

The overall survival (OS) was defined as the interval between the date of diagnosis to the date of death or date of last follow-up, and data were censored at December 31, 2012 from the date of MDS diagnosis. Survival curves were generated using Kaplan–Meier method and compared by log-rank test. Multivariate analysis was performed applying the Cox regression. All calculated *p* values are two sided, and *p* < .05 was considered statistically significant.

Fig. 1 Flow diagram of patient selection out of a total of 44,878 patients identified with Myelodysplastic syndrome (MDS), to arrive at those patients who were to be included in our survival analysis, within the SEER database during 2001–2012. *t*-MDS therapy-related MDS, *ICD* international classification of diseases for oncology

Table 1 The frequency and survival of t-MDS and de novo MDS according to demographics, calendar period, radiotherapy and causes of death, SEER-18, 2001–2012

Variable	All patients No. (%)	Frequency of MDS		<i>p</i> value [†]	Median OS (months)	
		t-MDS (<i>n</i> = 666)	De novo MDS (<i>n</i> = 29,703)		t-MDS	De novo MDS
Age (year)						
<70	9698 (31.9)	405 (60.8)	9293 (31.3)		17.96	53.00
70–79	9712 (32.0)	167 (25.1)	9545 (32.1)	0.000	15.06	33.14
+80	10,959 (36.1)	94 (14.1)	10,865 (36.6)		19.49 ^a	21.55 ^a
Median age in year (range)	76 (1–106)	65 (2–97)	76 (1–106)	0.000*	–	–
Median follow-up time in months (range)	21 (1–143)	16 (1–143)	21 (1–143)	–	–	–
Gender						
Male	16,746 (55.1)	324 (48.6)	16,422 (55.3)		15.00	27.56
Female	13,623 (44.9)	342 (51.4)	13,281 (44.7)	0.001	18.63	36.06 ^a
Race						
Caucasian	25,501 (84.0)	574 (86.2)	24,927 (83.9)		16.22	30.05
African-American	2409 (7.9)	57 (8.6)	2352 (7.9)	0.048	17.75	41.83 ^a
Asians	1953 (6.4)	26 (3.9)	1927 (6.5)		19.61	31.22
Others ^b	506 (1.7)	9 (1.4)	497 (1.7)		27.25 ^a	61.26
Marital status						
Un-married ^c	12,264 (40.4)	264 (39.6)	12,000 (40.4)		18.73	27.41
Married	15,323 (50.5)	350 (52.6)	14,973 (50.4)	0.35	15.39	32.11 ^a
Unknown	2782 (9.2)	52 (7.8)	2730 (9.2)		22.45 ^a	49.66
Calendar period						
2001–2006	14,018 (46.2)	322 (48.3)	13,696 (46.1)		17.67	32.09
2007–2012	16,351 (53.8)	344 (51.7)	16,007 (53.9)	0.25	16.85	30.08 ^a
Radiation						
No	29,739 (97.9)	637 (95.6)	29,102 (98.0)		17.28	31.09
Yes	240 (0.8)	21 (3.2)	219 (0.7)	0.000	27.50	31.54
Unknown	390 (1.3)	8 (1.2)	382 (1.3)		15.00	32.76
Causes of death (<i>n</i> = 19,632)						
AML-related death	2296 (11.7)	78 (15.0)	2218 (11.6)		–	–
Solid cancers	775 (3.9)	66 (12.7)	709 (3.7)	0.000	–	–
Others	16,561 (84.4)	377 (72.4)	16,184 (84.7)		–	–
Survival						
Median OS (months)	30.6	17.2	31.1		–	–
5-year OS (%)	32%	22%	32%	0.000	–	–

The bold values are statistically significant with *p* value <0.05

n number of cases, *t*-MDS therapy-related myelodysplastic syndrome, *AML* acute myeloid leukemia, *OS* overall survival, *CI* confidence interval, *SEER* surveillance, epidemiology, and end results

* Based on *Mann–Whitney U test*

† Based on *Chi square test*

^a Significant *log-rank test* (two-sided *p* value <0.05)

^b American Indian/Alaska Native, unknown

^c Single, separated, divorced, widowed, unmarried or domestic partner

Results and Discussion

Clinical Characteristics

I retrieved data 44,878 cases of MDS diagnosed in the eighteen U.S. population-based cancer registries

(2001–2012). There are 693 cases with t-MDS, which represent 1.5% of all subtypes of MDS. In USA Medicare study, among patients with MDS diagnosed during 2003, 4% had a history of chemoradiotherapy [9]. According to sequential exclusions that have shown in a Fig. 1, there are 666 patients (2.2%) with t-MDS, and 29,703 (97.8%) with

Table 2 Causes of death in deceased cases of therapy-related myelodysplastic syndrome (n = 521)

All-cause mortality	Deceased cases No. (%)
Blood cancers	210 (40.3%)
Acute myeloid leukemia	78 (37.1%)
Non Hodgkin lymphoma	64 (30.5%)
Hodgkin lymphoma	10 (4.8%)
Multiple myeloma	12 (5.7%)
Others	46 (21.9%)
Solid cancers	66 (12.7%)
Lung/bronchus	19 (28.8%)
Breast	11 (16.7%)
Ovary	10 (15.2%)
Colorectal	6 (9.1%)
Others	20 (30.2%)
Miscellaneous Cancer	120 (23%)
Non-cancer causes	91 (17.5%)
Other causes	31 (6%)
Unknown	3 (0.6%)
Total	521 (100%)

de novo MDS. The clinical and the survival outcomes of these cases are given in a Table 1.

In t-MDS cases, approximately two-third (60.8%) of the patients were younger than 70 years at the time of diagnosis, compared to approximately one third (31.3%) of patients with de novo MDS ($p < 0.001$). The median age of patients with t-MDS at presentation was 65 years (range 2–97 year), that was low compared with 76 years (range 1–106 year) for patients with de novo MDS ($p < 0.001$).

Women were more frequently affected than men in t-MDS, compared with patients with de novo MDS (51.4 vs. 44.7%, $p = 0.001$) (Table 1). In a large series, t-MDS/AML is more frequent in females, because of the high frequency of t-MDS/AML after treatment of breast cancer

[3, 4]. Smith et al. [3] reviewed 306 patients with t-MDS/t-AML treated at the University of Chicago; 32 patients (10%) have a history of breast cancers, and 19 patients (6.2%) with a history of ovary/uterus cancers. In a single institute study between 1980 and 2003, Rund et al. [4] reviewed 96 Jewish cases with t-MDS/AML, 30% of cases had a history of breast and ovarian cancers. In addition to chemoradiotherapy, granulocyte colony-stimulating factors are doubling the risk of t-MDS/AML in females with a breast cancers [10]. I found that, Asian race was more common in de novo MDS than t-MDS (6.5 vs. 3.9%, $p = 0.048$). Patients with t-MDS were more likely than de novo MDS to receive radiotherapy (3.2 vs. 0.7%, $p < 0.001$) (Table 1).

At presentation, 505 of 666 cases (75.8%) with t-MDS had a history of antecedent cancer, and 161 cases (24.2%) without antecedent cancer. The SEER database did not capture data regarding types of antecedent cancer. Noticeable, up to 22% of t-MDS/AML cases have a history of chemoradiotherapy for non-neoplastic diseases [11]. Furthermore, around 5% of t-MDS/AML was associated with autoimmune disorders [3, 12].

Causes of Death (COD)

In the overall patients ($n = 30,369$), with a median follow-up of 21 months (range 1–143 months), 19,632 (64.6%) patients died at last follow-up. Of these, 2296 cases (11.7%) died from AML and 775 cases (3.9%) died from solid cancers. One report pointed out that, AML accounted for 15% of deceased cases in a lower-Risk MDS [13]. Naqvi et al. [14] retrospectively analyzed 600 consecutive patients with MDS who presented to MD Anderson Cancer Center between 2002–2004; of these, 456 patients (76.0%) died and 123 patients (20.5%) evolved into AML.

In t-MDS cases, with a median follow-up of 16 months (range 1–143 months), 521 cases (78.2%) died; of which, 78 (15%) cases died from AML and 66 (12.7%) cases died from solid cancers (Table 1). In one report, 30% of t-AML

Table 3 Clinical features and outcome of subtypes of de novo myelodysplastic syndrome (n = 29,703)

Subtypes	No. (%)	Male No. (%)	Median age years (range)	Median survival (months)
Refractory anemia	3639 (12.3)	1809 (49.7)	75 (1–100)	48.3
Refractory anemia with sideroblasts	2698 (9.1)	1469 (54.4)	76 (1–99)	56.7
Refractory anemia with excess blasts	3927 (13.2)	2394 (61.0)	73 (1–100)	13.6
Refract. anemia with excess blasts in transformation	159 (0.5)	94 (59.1)	72 (4–100)	9.9
Refractory cytopenia with multilineage dysplasia	1758 (5.9)	1128 (64.2)	74 (1–99)	32.3
Myelodysplastic syndrome, NOS	17,522 (59.0)	9528 (54.4)	77 (1–106)	31.6

No number of cases, NOS not otherwise specified

Fig. 2 Kaplan–Meier estimates of overall survival of patients with MDS categorized by subtypes

had a prior history of t-MDS [5]. Of the total 66 cases died from solid cancers in t-MDS cases; 19 cases (28.8%) died from cancer of lung/bronchus, 11 cases (16.7%) breast cancers, and 10 cases (15.2%) ovarian cancer (Table 2). Solid cancer-related deaths were significantly more frequent in t-MDS compared to de novo MDS (12.7 vs. 3.7%, $p < 0.001$). Median age of deceased t-MDS cases was low compared to deceased de novo MDS (66 vs. 78 years, $p < 0.001$) [data not shown].

Survival and Prognosis

Regarding subtypes of de novo MDS, the poor survival had observed in refractory anemia with excess blasts in transformation (9.9 months), and refractory anemia with excess blasts (13.6 months) (Table 3).

In univariate analysis, median OS and 5-year OS of patients with t-MDS were significantly inferior compared to those with de novo MDS (17.2 months and 22% vs. 31.1 months and 32%, respectively, $p < 0.001$) (Table 1, Fig. 2). A two series pointed out that the median OS of t-MDS/AML was 8 to 10 months [3, 4]. In the current study, the 5-year OS was 22% (95% CI 19–25) that was very close to 22% (95% CI 19–29) of 323 t-AML cases received allogeneic transplants [5]. In the Chicago series ($n = 306$), the median OS after diagnosis of t-MDS/AML was 8 months and 5-years OS was less than 10% [3]. In a multivariate analysis adjusted for demographics, calendar

period and radiotherapy; patients with de novo MDS had better overall survival [adjusted hazard ratio (aHR) 0.59; 95% confidence interval (CI) 0.54–0.64, $p < 0.001$] than patients with t-MDS (Table 4; Fig. 2). Previous multivariate analyses showed that t-MDS/AML are unfavourable prognostic factors, independent of unfavorable cytogenetics [11, 12, 15]. Poor outcome of t-MDS/AML is related to persistence of the primary malignant disease, chronic immunosuppression from prior disease or on-going therapy, organ and bone marrow injury from prior therapy [1, 16]. In addition, t-MDS/AML patients had a high frequency of unfavourable cytogenetics compared to de novo MDS/AML [4, 17].

In this work, median survival times after the diagnosis of t-MDS by age group were 17.9 months for <70 years age group, 15 months for 70–79 age group, and 19.4 months for ≥ 80 years age group ($p = 0.013$). Moreover, patients aged <70 years had a favorable survival compared those aged ≥ 70 years (17.9 vs. 16 months, $p = 0.013$) (Fig. 3). It seems that the poor survival observed in the t-AML patients aged greater than or equal to 70 years old (16 months), was related to the poorest survival in age group 70–79 years old (15 months).

In the entire cohort, the risk of all-cause mortality in 70–79 years age group and ≥ 80 years age groups are 1.46-fold and 2.1-fold higher than those reported in <70 years age group ($p < 0.001$) (Table 4). Poor prognosis of old age is attributed to unfavourable cytogenetics, multidrug

Table 4 Prognostic factors of myelodysplastic syndrome outcome in a SEER database between 2001 and 2012 (n = 30,369)

Variables	Median OS months	5-year OS (%)	Multivariate analysis Hazard ratio (95% CI)	p value
All patients	30.6	32%		
Age (year)				
<70	50.58	46	1	
70–79	32.72	33	1.46 (1.41–1.52)	0.000
+80	21.53	19 ^a	2.10 (2.02–2.17)	0.000
Gender				
Male	27.26	29	1	
Female	35.44	36 ^a	0.78 (0.76–0.80)	0.000
Race				
Caucasian	29.66	31	1	
African-American	41.12	40	0.87 (0.83–0.92)	0.000
Asians	30.97	34	0.96 (0.91–1.02)	0.18
Other ^b	61.12	51 ^a	0.69 (0.60–0.78)	0.000
Marital status				
Un-married ^c	27.19	28	1	
Married	31.48	33 ^a	0.87 (0.84–0.90)	0.000
Unknown	49.13	44	0.65 (0.61–0.69)	0.000
MDS subtypes				
t-MDS	17.23	22	1	
De novo MDS	31.13	32 ^a	0.59 (0.54–0.64)	0.000
Calendar period				
2001–2006	31.62	33	1	
2007–2012	29.70	30 ^a	1.03 (1.00–1.06)	0.035
Radiotherapy				
No	30.64	32	1	
Yes	31.17	40	1.08 (0.91–1.28)	0.39
Unknown	32.16	29	1.11 (0.98–1.25)	0.10

n number of cases, t-MDS therapy-related myelodysplastic syndrome, OS overall survival, CI confidence interval, SEER surveillance, epidemiology, and end results

^a Significant *log-rank test* (two-sided *p* value <0.05)

^b American Indian/Alaska Native, unknown

^c Single, separated, divorced, widowed, unmarried or domestic partner

resistance, and co-morbidities [18]. Several reports showed that age is a risk factor for mortality in t-MDS/AML after autologous HSCT [5, 19]. In addition, age is one of parameters of prognostic scoring system for *denovo* MDS [20], and t-MDS [21].

In the current work, women have a long median survival compared to men (35.44 vs. 27.2 months, $p < 0.001$), and risk of all cause-mortality in women is 22% lower than men (aHR 0.78; 95% CI 0.76–0.80, $p < 0.001$) (Table 4). In a retrospective study of 1157 patients with primary MDS diagnosed by the German and Austrian MDS study group, age and gender had a

prognostic role [22]. In general, I observed that female-sex is a lucky variable outcome in several blood cancers [23, 24]. Finally, unmarried patients ($p < 0.001$) and the recent years of diagnosis ($p = 0.035$) are unfavourable prognostic factors (Table 4).

This SEER analysis had limitations, such as, lack of information regarding types of primary cancers, prior therapy, and cytogenetics. However, our cohort is a population-based that provides a valuable data regarding clinical prognostic factors, and survival outcomes.

In conclusion, t-MDS is different from *de novo* MDS in terms of clinical features and outcomes.

Fig. 3 Kaplan–Meier estimates of overall survival of patients with t-MDS categorized by age group

Compliance with Ethical Standards

Conflict of interest No conflicts of interest.

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