Hematology/Oncology and Stem Cell Therapy

Volume 15 | Issue 1 Article 5

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Recommended Citation

Nampoothiri, Ram Vasudevan; Law, Arjun Datt; Lam, Wilson; Chen, Carol; Al-Shaibani, Zeyad; Loach, David; Michelis, Fotios V.; Kim, Dennis Dong Hwan; Mattsson, Jonas; Kumar, Rajat; Lipton, Jeffrey Howard; and Viswabandya, Auro (2022) "Predictors of Outcomes of Therapy-Related Acute Myeloid Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation," *Hematology/Oncology and Stem Cell Therapy*: Vol. 15 : Iss. 1 , Article 5.
Available at: https://doi.org/10.1016/j.hemonc.2021.03.003

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ORIGINAL RESEARCH REPORT

Predictors of Outcomes of Therapy-Related Acute Myeloid Leukemia After Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Background/Objective: **Existing literature on allogeneic hematopoietic stem cell transplantation (allo-HSCT) in therapy-related acute myeloid leukemia (t-AML) is confounded by the inclusion of patients with secondary AML and t-MDS. We aim to report our 20-year experience of HSCT in t-AML.**

Methods: **We retrospectively reviewed patients with t-AML who underwent HSCT. Patients were analyzed for prior malignancy, therapy, time to diagnosis of t-AML, transplant details, relapse-free survival (RFS), overall survival (OS), and predictors of outcomes.**

Results: **In total, 68 patients (59.9% female; median age, 56.5 years) underwent HSCT. Acute and chronic graft-versus-host disease (GVHD) occurred in 39 (57.4%) and 23 (33.8%) patients, respectively. Cumulative incidence of relapse, nonrelapse mortality, RFS, and OS at 2 years were 17.9%, 34.5%, 47.6%, and 49.3%, respectively. Significant predictors of reduced OS were presence of 11q23 rearrangement (hazard ratio [HR], 3.24), using induction regimens other than FLAG-Ida or 7 + 3 (HR, 3.65), haploidentical donors (HR, 3.48), Eastern Cooperative Oncology Group performance status 2 or higher (HR, 5.83), and using cyclosporine A−methotrexate as GVHD prophylaxis (HR, 2.41). A significant decrement in survival was seen with an increasing number of any of these prognostic factors.**

Conclusion: **Outcomes of t-AML are satisfactory after allo-HSCT. Patients with t-AML with good-risk karyotypes, good performance status, having HLA-matched donors, and receiving intensive induction regimens have better outcomes after HSCT.**

Keywords: Allogeneic hematopoietic stem cell transplantation, Prognostic factors, Therapy-related acute myeloid leukemia

1. Introduction

Therapy-related acute myeloid leukemia (t-AML) is a rare but well-known complication after exposure to cytotoxic chemotherapy and/or radiotherapy (RT) for previous cancer or nonmalignant disorders [1]. The prevalence of t-AML across studies is around 10−15% of all AML cases [2,3]. The incidence of t-AML is increasing because of longer life expectancy of the general population and also because of the improved survival of patients treated with chemotherapy and/or radiation for prior malignancies [4].

Patients with t-AML are known to have an increased frequency of adverse cytogenetic (like chromosome 5 and/or 7 abnormalities, complex karyotype) [5−7] as well as molecular abnormalities (like TP53 mutations) [8,9]. In view of the unique adverse prognostic features, aggressive clinical course, and distinct etiology, therapy-related myelodysplastic syndrome (t-MDS) and t-AML have

Received 18 November 2020; revised 29 January 2021; accepted 6 March 2021.
Available online 1 March 2022

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https://doi.org/10.1016/j.hemonc.2021.03.003

been classified together as a separate entity called "therapy-related myeloid neoplasms (t-MN)" in the latest classification of myeloid neoplasms by the World Health Organization [10]. However, there is evidence that the outcomes of t-MDS and t-AML are not necessarily similar, with worse outcomes in the more aggressive t-AML group [11,12]. There is also literature that proposes different prognostic variables and scores for outcomes in t-MDS [13].

The prognosis of t-AML is poor with standard chemotherapy, with median overall survival (OS) ranging from 5 months to 16 months [12,14]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers a chance of sustained disease-free survival in a proportion of patients with t-AML [15,16]. Existing literature on allo-HSCT in t-AML is confounded not only by the inclusion of t-MDS and/or secondary AML (transformed from MDS or myeloproliferative neoplasms) but also by the inclusion of t-AML undergoing HSCT with active disease [17]. Therefore, the outcomes and predictors of outcomes specific to t-AML in remission after allo-HSCT are largely unknown. Here we present our 20-year experience on the outcomes and predictors of outcomes of allo-HSCT in adults with t-AML in complete morphological remission.

2. Patients and methods

Adult patients with AML who underwent allo-HSCT at the Princess Margaret Cancer Centre, Toronto, Canada from 1999 to 2019, were screened to identify cases of t-AML. t-AML was defined as AML occurring after prior exposure to cytotoxic chemotherapy and/or radiation. Patients with AML with a prior malignancy but no exposure to cytotoxic therapy were excluded. Patients with genetic syndromes predisposing them to leukemia (e.g., Fanconi anemia) and patients with hematological malignancies known to progress to AML (like myeloproliferative neoplasms) were also excluded. All patients were in complete morphological remission (defined as bone marrow aspirate showing less than 5% blasts with no clusters of blasts in trephine biopsy) at the time of allo-HSCT. The study was approved by the Research Ethics Board at the University Health Network, Toronto, Canada. Disease and treatment characteristics including previous malignancy, cytotoxic exposure, cytogenetic and molecular abnormalities, as well as transplantation details, were collected from electronic patient records. We calculated survival statistics using the Kaplan–Meier method and used a log-rank test to compare survival outcomes between groups. We used the Cox proportional hazards model to identify predictors of survival outcomes. We used a univariate regression model initially and used a p value < 0.1 as cut-off to include variables in the multivariable Cox regression model. OS was defined as the time from transplant to date of death from any cause or date of last follow-up. Relapse-free survival (RFS) was defined as the time from transplant to date of AML relapse or death from any cause. Nonrelapse mortality (NRM) was measured from the time of transplant to death from any cause in the absence of relapse. AML relapse was treated as a competing event for NRM. Cumulative incidence of relapse (CIR) was measured as the time from transplant to relapse with death from any cause other than relapse as a competing event. All analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

During the study period from January 1999 to December 2019, 68 adults with t-AML (59.9% females; $n = 38$) underwent allo-HSCT at our center. The median (range) age at the time of allo-HSCT was 56.5 (18–72) years. The most common malignancies for which cytotoxic chemotherapy/RT was given prior to the onset of AML were carcinoma of the breast in 16 (23.5%) patients and non-Hodgkin lymphoma in 13 (19.1%) patients. A total of 35 (52.2%) patients received RT, of which 12 (17.6%) patients received RT as their only form of cancer treatment. Previous chemotherapy received by patients with t-AML included alkylating agents and topoisomerase inhibitors in 39 (60%) and 29 (44.6%) patients, respectively.

The median (range) latent period of diagnosis of t-AML from time of cytotoxic chemotherapy/RT exposure was 73 (15–377) months. Identifiable cytogenetic abnormalities were present in 34 (54.8%) patients, whereas eight (12.9%) patients had inconclusive cytogenetics and 20 (32.3%) patients had normal cytogenetics. Complex karyotype was the most common cytogenetic abnormality seen in 12 (19.4%) patients, followed by rearrangement in the 11q23 locus (KMT2A − MLL gene) seen in 11 (17.7%) patients. There was a positive correlation (Pearson correlation coefficient 0.27; $p = .04$) of the presence of 11q23 rearrangement with exposure to topoisomerase inhibitors. Patients with 11q23 rearrangement had a shorter latent period for the development of t-AML after cytotoxic chemotherapy/RT than patients with a complex karyotype (median: 50 months vs. 154 months; $p = .02$). Based on cytogenetic risk stratification (ELN 2017), 23 (37.1%) patients had high-risk cytogenetics and 35 (56.5%) patients had

intermediate-risk cytogenetics at diagnosis of t-AML. Induction protocols used for remission induction were FLAG-Ida and cytarabine–daunorubicin (7 + 3) in 29 (44%) patients, each while eight (12%) patients received other regimens (including azacytidine and gemtuzumab ozogamicin). A total of 10 (15.4%) patients required more than one induction to achieve morphological remission. Baseline characteristics are shown in Table 1.

The median (range) time to transplant from diagnosis of t-AML was 6 (2–22) months. Matched sibling donors were used in 26 (38.2%) patients, matched unrelated donors in 37 (54.4%) patients, and haploidentical donors in five (7.4%) patients. Performance status was Eastern Cooperative Oncology Group (ECOG) score 0–1 in 51 (75%) patients and score 2 in 17 (25%) patients. Myeloablative conditioning was used in 30 (44.1%) patients and reduced-intensity conditioning in 38 (55.9%) patients. Graft-versus-host disease (GVHD) prophylaxis regimens consisted of antithymocyte globulin with post-transplant cyclophosphamide and cyclosporine A (CSA) in 19 (27.9%) patients, and CSA with either mycophenolate or methotrexate (MTX) in 14 (20.6%) patients each. Median (range) day of neutrophil engraftment was 17 (5–41) days, and patients were discharged after a median (range) stay in hospital of 22 (6–84) days after allo-HSCT. Transplant characteristics, donor details, and post-transplant complications are depicted in Table 2.

Grade 2–4 acute GVHD was seen in 39 (57.4%) patients. Chronic GVHD of any site and severity was seen in 23 (33.8%) patients. During the study period, 14 (20.6%) patients relapsed, of which four

Table 1. Prior Malignancies and Baseline Characteristics of Patients with Therapy-related Acute Myeloid Leukemia.

Prior diseases	***n* (%)**
Nonhematological malignancies	27 (39.7)
Ca breast	16 (23.5)
Thyroid	2 (2.9)
Soft tissue sarcoma	3 (4.4)
Hematological malignancies	28 (41.1)
Multiple myeloma	6 (8.8)
Non Hodgkin lymphoma	13 (19.1)
Hodgkin lymphoma	9 (13.2)
Nonmalignant disease	13 (19.1)
Rheumatoid arthritis	4 (5.9)
Organ transplant	2 (2.9)
Inflammatory bowel disease	3 (4.4)
Other autoimmune diseases	4 (5.9)
Treatment received	***n* (%)**
Radiotherapy	35 (52.2)
Radiotherapy alone	12 (17.9)
Alkylator exposure	39 (60)
Topoisomerase inhibitor exposure	29 (44.6)
Both alkylators & topoisomerase inhibitors	27 (41.5)
Autologous HSCT	12 (17.6)
Cytogenetic abnormalities	***n* (%)**
11q23 rearrangement	11 (17.7)
Complex/monosomal karyotype	12 (19.4)
Inconclusive cytogenetics	8 (12.9)
Deletion 7	9 (14.5)
Normal karyotype	20 (32.3)
Induction regimens	***n* (%)**
Cytarabine and daunorubicin (7 + 3)	29 (43.9)
FLAG-Ida	29 (43.9)
Others	8 (12.2)
Inductions needed to attain remission	***n* (%)**
Remission after 1 induction cycle	55 (84.6)
Remission after > 1 induction cycle	10 (15.4)
Remission status	***n* (%)**
First completed remission	63 (92.6)
Second complete remission	5 (7.4)

Note. Ca = carcinoma; HSCT = hematopoietic stem cell transplantation.

Table 2. Pre-transplant donor and recipient characteristics and post-transplant complications in patients with therapy-related acute myeloid leukemia.

Donors	***n* (%)**
Matched sibling donor	26 (38.2)
Matched unrelated donor	37 (54.4)
Haploidentical donor	5 (7.4)
Blood group match	***n* (%)**
Matched blood group	19 (48.7)
Major or bidirectional mismatch	15 (38.5)
Minor mismatch	5 (12.8)
Pre-HSCT ECOG performance status score	***n* (%)**
0–1	51 (75)
2	17 (25)
Conditioning regimens received	***n* (%)**
Flu(4) + Bu(2) + TBI(200)	38 (55.9)
Flu(4) + Bu(4) + TBI(400)	15 (22.1)
Cy-TBI	6 (8.8)
Flu(4) + Bu(4)	3 (4.4)
Others	6 (8.8)
GVHD prophylactic regimens used	***n* (%)**
CSA–methotrexate	14 (20.6)
Campath–CSA	12 (17.6)
ATG–PTCy–CSA	19 (27.9)
CSA–mycophenolate	14 (20.6)
Others	9 (13.2)
Post-HSCT complications	***n* (%)**
SOS/VOD	9 (13.4)
CMV reactivation, *n* (%)	27 (49.1)

Note. ATG = antithymocyte globulin; Bu = busulphan; CMV = cytomegalovirus; CSA = cyclosporine A; ECOG = Eastern Cooperative Oncology Group; Flu = fludarabine; HSCT = hematopoietic stem cell transplantation; PTCy = post-transplant cyclophosphamide; SOS/VOD = sinusoidal obstruction syndrome/veno-occlusive disease; TBI = total body irradiation.

(28.6%) patients relapsed within D + 100 of allo-HSCT. During the 20-year study period, 39 (57.4%) patients died with early deaths (by D + 100) occurring in nine (13.2%) patients. Early deaths were due to refractory acute GVHD in two (22.2%) patients, severe sepsis with multiorgan dysfunction in four (44.4%) patients, thrombotic microangiopathy with pulmonary hemorrhage in one (11.1%) patient, and relapse in two (22.2%) patients. None of the patients had a relapse of primary malignancy after allo-HSCT. The median follow-up duration was 21 months in patients surviving after D + 100. The 2-year estimated CIR and NRM were 17.9% and 34.5%, respectively, while 2-year RFS and OS were 47.6% and 49.3%, respectively (Fig. 1A and 1B).

We examined categorical and continuous variables like age, sex, presence of 11q23 or complex cytogenetics, exposure to alkylators or topoisomerase inhibitors, performance status prior to transplant, donor type, conditioning regimen intensity, GVHD prophylaxis regimens, the latent period before a diagnosis of t-AML, and other parameters for factors predictive for better OS after allo-HSCT. Factors significantly associated with better OS on univariate analysis are given in Table 3. After multivariate Cox regression analysis, multiple factors were found to predict poor OS (Table 4). Pre-transplant factors like presence of 11q23 rearrangement (hazard ratio [HR], 3.24; $p = .007$), using induction regimens other than FLAG-Ida or 7 + 3 (HR, 3.65; $p = .005$), having a haploidentical donor (HR, 3.48; $p = .02$), and ECOG performance status ≥ 2 (HR, 5.83; $p < .001$) were predictive of poor OS. Use of CSA–MTX GVHD prophylaxis (HR, 2.41; $p = .018$) was the post-transplant factor predictive for poor OS after multivariate Cox regression analysis. Delayed neutrophil engraftment (beyond D + 18) was another post-transplant factor associated with poor OS ($p = .002$). The presence of any one of these factors resulted in an added adverse effect on survival. There was a significant decrement in survival with an increasing number of any of the prognostic factors. Patients with no risk factors and one risk factor had a 2-year OS of 77.6% and 46.9%, respectively, whereas patients with two to four risk factors had an estimated 2-year OS of only 6.2% ($p < .001$).

4. Discussion

Initially, t-AML was described in patients who had prior exposure to the alkylating agent melphalan for multiple myeloma [18]. Later, it was described in patients after RT as well as exposure to topoisomerase inhibitors [19]. This initially led to a classification within t-MN based on the prior exposure (alkylators vs. topoisomerase inhibitors) with different latent periods, responses to therapy, and characteristic cytogenetic abnormalities in each group [5]. This subclassification was later abandoned in view of prior exposure of most patients to both lines of chemotherapy as part of combination chemotherapy regimens [20]. Bacher et al. [11] suggested that although t-MDS and t-AML had similar cytogenetic and molecular mutation profiles, they showed different biological characteristics and

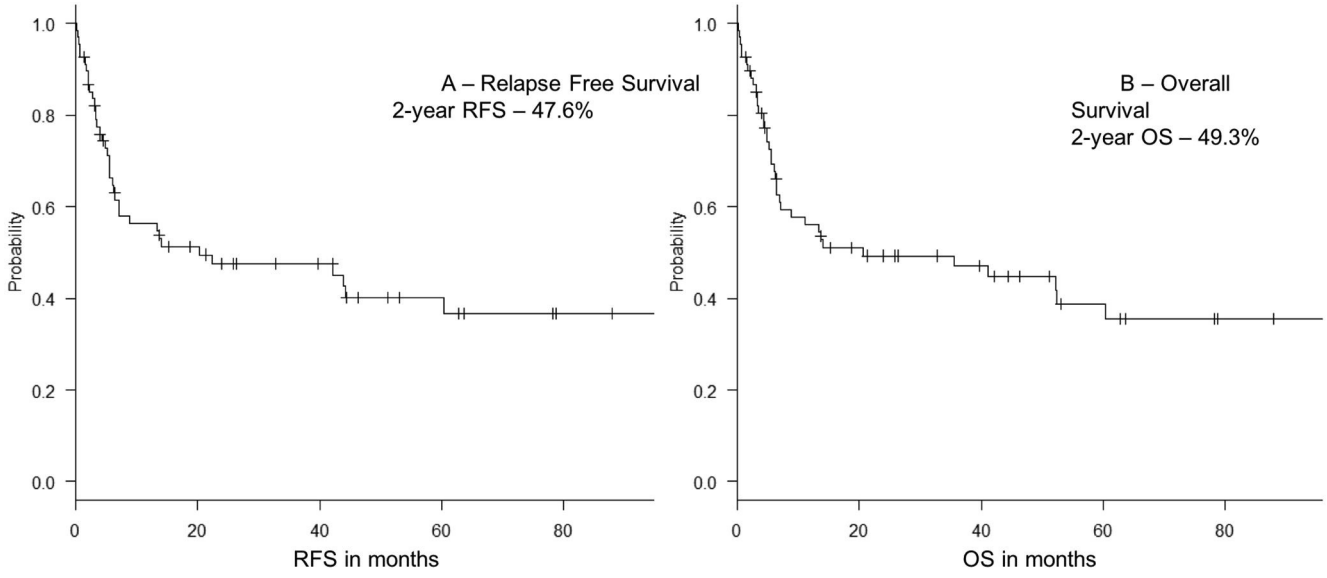

Fig. 1. Kaplan–Meier curves for (A) relapse-free survival (RFS) and (B) overall survival (OS) of patients with therapy-related acute myeloid leukemia after allogeneic stem cell transplantation.

Table 3. Predictive factors for poor overall survival after univariate analysis.

Factor		Median estimated survival (months)	*p*
Time of transplant	HSCT before 2010	8.9	0.043
	HSCT after 2010	99	
Nonmalignant disease	Cytotoxic therapy for nonmalignant disease	NR	0.105
	Cytotoxic therapy for malignancy		
		11	
Monosomy chromosome 7	Monosomy present	7	0.009
	No monosomy	52.5	
11q23 rearrangement	Rearrangement present	4.8	0.011
	No rearrangement	52.2	
Abnormal karyotype	Any abnormal karyotype	7.1	0.058
	Normal karyotype	98.6	
Induction chemotherapy	7 + 3 induction	20.7	0.042
	FLAG-Ida induction	NR	
	Other regimens	3.3	
Donor	Matched-related/unrelated donor	35.6	0.05
	Haploidentical donor	5.5	
Performance status at HSCT	ECOG 0–1	60.4	<0.001
	ECOG 2	6.1	
Conditioning regimens	Myeloablative conditioning	13.4	0.194
	Reduced intensity conditioning	52.2	
GVHD prophylaxis	CSA–MTX prophylaxis	5.5	0.003
	Other prophylactic regimens	52.5	
Post-transplant SOS/VOD	Patients with SOS/VOD (any severity)	6.4	0.006
	Patients without VOD	52.5	
Neutrophil Engraftment	NE $\leq$ 18 days	98.6	0.003
	NE > 18 days	6.4	

Note. CSA = cyclosporine A; ECOG = Eastern Cooperative Oncology Group; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; MTX = methotrexate; NE = neutrophil engraftment; NR = not reached; SOS/VOD = sinusoidal occlusion syndrome/veno-occlusive disease.

treatment outcomes. Significantly lower survival in patients with t-AML developing from t-MDS when compared to patients with t-MDS after allo-HSCT was reported by Chang et al. [21] in their study on outcomes of secondary MDS. Therefore, we hypothesized that the outcomes of t-MDS were different from those of t-AML after allo-HSCT in view of all patients with t-AML requiring induction chemotherapy and, in general, having more aggressive disease.

The proportion of abnormal karyotype is higher in patients with t-AML than in patients with *de novo* AML with an increased prevalence of adverse-risk cytogenetics [5–7]. While some studies suggest that the increased proportion of poor-risk cytogenetics and molecular abnormalities (like TP53 mutations) are responsible for the overall poor prognosis of t-AML [16,22], other studies propose that prior cytotoxic therapy itself is a poor prognostic marker irrespective of cytogenetic and molecular abnormalities [6]. Studies in patients with t-AML after allo-HSCT have almost uniformly shown worse prognosis in patients with high-risk cytogenetics [16]. The Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of 868 patients with t-MDS/AML showed that the prognostic impact of poor-risk cytogenetics persisted even after allo-HSCT [15]. The European Society for Blood and Marrow Transplantation (EBMT) data on allo-HSCT in patients with t-MDS/AML showed that presence of any abnormal karyotype (excluding favorable-risk cytogenetics) was a detrimental prognostic indicator [22]. In our cohort of t-AML patients in morphological remission, any abnormal karyotype

Table 4. Predictive factors for poor overall survival after multivariate cox regression analysis.

Factor	HR (95% CI)	*p*
11q23 rearrangement	3.24 (1.4–7.7)	0.007
ECOG performance status score 2	5.83 (2.6–13.1)	<0.001
Haploidentical donor	3.48 (1.2–10.0)	0.02
CSA–MTX GVHD prophylaxis	2.41 (1.2–5.0)	0.018
Induction regimens other than 7 + 3/FLAG-Ida	3.65 (1.5–9.0)	0.005

Note. CI = confidence interval; CSA = cyclosporine A; ECOG = Eastern Cooperative Oncology Group; GVHD = graft-versus-host disease; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; MTX = methotrexate.

or the presence of high-risk chromosomal abnormalities like del-7 or 11q23 rearrangements were predictive of poor outcomes in univariate analysis. However, only the presence of 11q23 rearrangements retained its prognostic significance after multivariate Cox regression analysis. Bacher et al. [11] have earlier demonstrated that t-AML patients with 11q23 rearrangement (MLL-PTD positive) had worse OS (median: 2.5 months vs. 27.0 months; $p = 0.001$) than patients without the same. The associations of the presence of 11q23 rearrangements with the previous history of exposure of topoisomerase inhibitors [23,24] and shorter latent period to the development of t-AML [25], as seen in our study, are previously well described.

We reported a 2-year NRM of 34.5%. The French Society of Bone Marrow Transplantation has reported a 2-year NRM of 49% after allo-HSCT in t-MDS/AML [26]. The CIBMTR data on allo-HSCT in t-MDS/AML also showed 49% NRM in 5 years [15], while the multicenter study by Kayser et al. [7] reported a 4-year NRM of 38.5% after allo-HSCT in t-AML patients. The NRM after allo-HSCT in t-AML is likely to be higher than that in *de novo* AML due to multiple factors including poor hematopoietic reserve, poor tolerance for acute toxicity of treatment, chronic immunosuppression from previous therapy, and transfusion refractoriness [27,28]. Anderson et al. [29] described a 5-year NRM of 44.3% after allo-HSCT in secondary AML (AML after MDS/t-AML) and noted that a shorter interval from diagnosis to transplant was associated with lower NRM. Our data showed detrimental outcomes and possibly increased D + 100 transplant-related mortality in patients having delayed neutrophil engraftment (>D + 18). Although similar data is not available in the setting of t-AML, overall delayed engraftment is associated with poor outcomes after allo-HSCT [30]. Due to improvements in modern supportive care (including the widespread use of colony-stimulating factors) and changes in GVHD prophylaxis, NRM after allo-HSCT is decreasing [31]. Improvement of NRM with every year of transplant was also shown by data from the EBMT after allo-HSCT in t-MDS/AML, which showed 3-year NRM to be 37% [22]. Chang et al. [21] also demonstrated an improving NRM every year after allo-HSCT in secondary MDS/t-AML. Similar results could also be demonstrated in our cohort in univariate analysis with HSCT performed after 2010 having better outcomes than those performed before 2010.

The 2-year OS of 49.3% in patients with t-AML undergoing HSCT in our cohort seems favorable when compared to published literature. Early data from Fred Hutchinson Cancer Centre after allo-HSCT in t-AML showed a 5-year OS of 24.4% [29]. The French Society of Bone Marrow Transplantation reported a 2-year OS of 30% [26], while the CIBMTR cohort had a 5-year OS of 22% after HSCT in t-MDS/AML [15]. Comparable with our outcomes, Fianchi et al. [3] published a median OS of 58.8 months after allo-HSCT in t-MDS/AML. They also reported that the outcomes were significantly better than those of patients treated with other modalities [3]. The EBMT group initially published outcomes of patients with t-MDS/AML transplanted from HLA-identical siblings. They reported a 35% 3-year disease-free survival after allo-HSCT in these patients [32]. Subsequently, a follow-up study from the same registry reported a 3-year event-free survival and OS of 33% and 35%, respectively [22]. The reasons for the discrepancy in outcomes could be because our cohort is a selective cohort of t-AML in morphological remission with the exclusion of t-MDS, other secondary AML, and AML not in remission.

The factors associated with better OS in our study (Table 4), that is, absence of 11q23 rearrangement, better ECOG performance status, presence of HLA-matched donor, receiving 7 + 3/FLAG-Ida induction regimens, and using GVHD prophylaxis other than CSA−MTX, are also somewhat different from previously reported literature. Data from CIBMTR and EBMT are not only confounded by the inclusion of t-MDS but also by the inclusion of t-AML not in remission (26% and 38% of patients, respectively) at the time of HSCT. Both the CIBMTR and EBMT data on allo-HSCT in t-MDS/AML suggest inadequate disease control at the time of transplant as a risk factor for poor outcomes [15,22]. This can also explain the poor outcomes in our cohort of patients who received less intense induction regimens (other than 7 + 3/FLAG-Ida) as they may have been in a lesser degree of disease control than patients who received intensive conditioning regimens. Lack of minimal residual disease (MRD) data prevents us from making definitive conclusions on the same. Our prognostic model has pre- and post-transplant variables, each with an additive detrimental effect on overall outcomes. Therefore, alternative treatment options may be considered in patients having a higher number of risk factors.

Younger age has been found to be favorable for outcomes in t-AML after allo-HSCT across multiple reports [22,26]. Better performance status, and not chronological age, correlated with favorable outcomes in our cohort. A multicenter study incorporating all AML patients treated with standardized chemotherapy according to the GIMEMA protocols

showed that t-AML patients with good performance status had response rates and survival similar to *de novo* AML [33]. The performance status of patients has not been assessed in the larger registry studies for HSCT in t-AML. With the increasing significance of frailty and functional assessment in the prognosis of patients undergoing allo-HSCT [34], we propose that patients with good performance status and lower frailty scores are likely to have favorable outcomes after allo-HSCT in t-AML.

There is a dearth of literature looking into the prognostic impact of GVHD prophylactic regimes in the outcomes after allo-HSCT in t-AML. However, there is data to suggest that modern GVHD prophylactic regimens incorporating a more frequent usage of drugs like mycopheloate mofetil, antithymocyte globulin, and/or post-transplant cyclophosphamide results in improved OS and GVHD-free RFS [35]. The same reflects in our study with improved outcomes in patients using non-CSA–MTX GVHD prophylactic regimens.

Our study is limited by the retrospective data collection of patients spread over 20 years. This may lead to a bias, given the evolving treatment modalities for the primary malignancies as well as changes in transplant-related parameters including conditioning regimens and drugs used for GVHD prophylaxis. Although cytogenetic data is available for 91% of patients in the study, molecular and next-generation sequencing (NGS) data, along with MRD monitoring data are not available for the majority of patients with t-AML. t-MNs are grossly underrepresented in clinical trials [36], and there is a paucity of prospective data on the effect of HSCT in these patients. The proportion of secondary AML included in EORTC–GIMEMA trials over 14 years was only 1.5% of all AML, while the prevalence of the same registered at the same time was at least 6% [37]. Within the MRC AML-10, 11, and 12 trials, t-AML accounts for only 2.3% of all AML patients [6]. This points toward a selection bias in clinical trials excluding patients with t-AML. Prospective studies with NGS data (both at the time of primary malignancy and at time of t-AML diagnosis) may be able to distinguish patients who are truly therapy-related from those patients in whom the AML occurred as a stochastic event (occurring by chance) or as part of an inherited genetic predisposition. Such studies will also present prognostic markers specific to patients with t-AML.

In conclusion, t-AML is an increasingly prevalent disease with poor prognosis; however, outcomes are acceptable after allo-HSCT. Patients of t-AML having good-risk karyotypes, good performance status, and having HLA-matched donors have favorable outcomes after allo-HSCT. Intensive induction regimens and improving supportive care with time also contribute to improving outcomes of HSCT in t-AML.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ram Vasudevan Nampoothiri: . **Arjun Datt Law:** . **Wilson Lam:** Supervision. **Carol Chen:** Formal analysis. **Zeyad Al-Shaibani:** Supervision, Writing - review & editing. **David Loach:** Supervision, Writing - review & editing. **Fotios V. Michelis:** Supervision, Writing - review & editing. **Dennis (Dong Hwan) Kim:** Supervision, Writing - review & editing. **Jonas Mattsson:** Supervision, Writing - review & editing. **Rajat Kumar:** Supervision, Writing - review & editing. **Jeffrey Howard Lipton:** Supervision, Writing - review & editing. **Auro Viswabandya:** Conceptualization.

Acknowledgments

The authors would like to acknowledge the immense importance of our BMT data coordinators. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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