HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Letter
Open Access

Primary Cancer Matters in Therapy-related Myeloid Neoplasm Patients Receiving Allogeneic Hematopoietic Cell Transplantation: A Study From the Chronic Malignancies Working Party of the EBMT

Marie Robin[1], Liesbeth C. de Wreede[2], Thomas Schroeder[3], Friedrich Stölzel[4], Nicolaus Kröger[5], Linda Koster[2], Uwe Platzbecker[6], Jürgen Finke[7], Arnold Ganser[8], Didier Blaise[9], Fabio Ciceri[10], Johan Maertens[11], Hélène Labussière Wallet[12], Junfeng Wang[2], Patrice Chevallier[13], Jakob Passweg[14], Jan J Cornelissen[15], Stéphanie Nguyen[16], Edouard Forcade[17], Amandine Charbonnier[18], Francesca Bonifazi[19], Patrick Hayden[20], Donal P. McLornan[21], Ibrahim Yakoub-Agha[22]

Correspondence: Marie Robin (marie.robin@aphp.fr).

Therapy-related myeloid neoplasms (t-MN) encompass a group of diseases, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), occurring after chemotherapy or radiation used to treat another cancer, either solid tumor (ST) or hematological malignancy, or less often another disease entity, for example, autoimmune disorders. For instance, it is estimated that the cumulative 10-year incidence of t-MN after breast cancer is 0.5% (reviewed in reference 1). The number of these t-MNs is expected to grow with the increase of life expectancy after cancer therapy, since they occur several years after chemotherapy. The prognosis of t-MN is dismal, and life expectancy is lower than in de novo myeloid disease.[2] Consequently, patients <75 years lacking multiple comorbidities are regularly referred for consideration of allogeneic hematopoietic cell transplant (allo-HCT), which remains the only curative option. While the median age at t-MN diagnosis is 65 years, and many of these individuals may have several comorbidities, a minority may be eligible for allo-HCT. A large Swedish registry based analysis reported that 20% of therapy-related AML patients could be transplanted.[3] During the last decade, large studies based on international registries have reported that 3-year relapse-free survival (RFS) from the date of allo-HCT is estimated between 25% and 33%.[4–7] Outcomes after allo-HCT have progressively improved over time, with a recent European Society for Blood and Marrow Transplantation (EBMT) study demonstrating a 2-year overall survival (OS) of 44% in patients with secondary leukemia (79% of them post-myeloproliferative neoplasm [MPN] or post-MDS).[8] Our group recently reported that the primary hematological disease impacts the outcome following allo-HCT in patients with AML arising from MDS, MPN, and chronic myelomonocytic leukemia, and that patients with a previous MPN had a worse outcome.[9] In addition to the primary hematological disease, these previous reports identified the following risk factors for mortality: older age, leukemia disease status at time of allo-HCT, cytogenetics, Karnofsky score, and utilization of an alternative donor. The recent Center for International Blood and Marrow Transplant Research (CIBMTR) report identified age, disease risk, and previous autologous HSCT as risk factors for outcome.[6] We hereby report outcomes following allo-HCT for t-MN occurring after nonmyeloid disease and determine if the primary cancer impacts outcomes.

[1]Hôpital Saint-Louis, APHP, Université de Paris Cité, France
[2]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands
[3]Department of Hematology and Stem cell Transplantation, West German Cancer Center, University Hospital of Essen, Germany
[4]University Hospital, Dresden, Germany
[5]University Medical Center Hamburg-Eppendorf, Germany
[6]University Hospital Leipzig, Germany
[7]University of Freiburg Medical Center and Medical Faculty, Freiburg, Germany
[8]Hannover Medical School, Hannover, Germany
[9]Institut Paoli Calmettes, Marseille, France
[10]IRCCS San Raffaele Scientific Institute, Milan, Italy
[11]University Hospital Gasthuisberg, Leuven, Belgium
[12]Hôpital Lyon Sud, Hospices Civiles de Lyon, Pierre Benite, France
[13]University Hospital, Nantes, France
[14]University Hospital, Basel, Switzerland
[15]Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands
[16]Hôpital de La Pitié Salpétrière, APHP, Paris, France
[17]CHU Bordeaux, France
[18]CHU Amiens, France
[19]IRCCS Azienda Ospedaliero-Universitaria di Bologna, France
[20]St James Hospital, Dublin, Ireland
[21]University College Hospital, London, United Kingdom
[22]CHU Lille, Lille, Univ Lille, INSERM U1286, Infinite, France

Supplemental digital content is available for this article.

HemaSphere (2023) 7:3(e851).
http://dx.doi.org/10.1097/HS9.0000000000000851.
Received: August 23, 2022 / Accepted: January 27, 2023

The study was approved and conducted by the Chronic Malignancies Working Party of the EBMT. From the EBMT registry, patients 18 years or older at time of allo-HCT, with MDS or AML occurring after therapy for a primary cancer who underwent allo-HCT between 2006 and 2016 were included. Patients who had AML secondary to MDS or MPN were excluded.

We identified 2334 patients with t-MN, either AML (n = 1353) or MDS (n = 981). MDS was classified with excess blasts in 505 (52%) patients (unknown in 20 patients). Median age at time of allo-HCT was 57 years (range, 18–79). Among patients where Karnofsky score had been annotated (n = 2066), the majority had a Karnofsky score of 90 or higher (n = 1376; 67%). Primary cancers were chronic lymphocytic leukemia (CLL) in 102 (4%), non-Hodgkin lymphoma (NHL) in 668 (29%), Hodgkin lymphoma (HL) in 235 (10%), plasma cell disease (PCD) in 111 (5%), breast cancer in 643 (28%), and other ST in 575 (25%). Median interval between the primary cancer and the t-MN was 59 months (interquartile range [IQR]: 30–109) and median time between t-MN diagnosis and HCT was 5.7 months (IQR: 4.1–9.1). There was a higher proportion of patients with a previous autologous HCT in patients with PCD (82%), HL (59%), and NHL (52%) compared with patients with CLL (20%), breast cancer (1%), or other ST (5%) as primary diagnosis. An HLA-matched sibling donor (SIB) was the donor in 722 (31%) patients, all other patients received a transplant from an unrelated donor (information missing in 4 patients). Some variables were unwell balanced according to the type of donor, especially age, type of disease, regimen intensity, use of total body irradiation, disease status, and time from t-MN to transplantation (Suppl. Table 1S). The conditioning regimen was myeloablative conditioning regimen (MAC) in 843 (36%). Disease status (missing in 66 patients) was associated with the type of disease: 30% of MDS (95% confidence interval [CI], 28%-34%) and 77% of AML patients (95% CI: 74%-79%) were in complete remission (CR) at time of allo-HCT ($P < 0.001$). Most of the AML patients in CR were in first CR (902 patients, 68%), the remainder were in CR2 (8%) or in CR without further specification (1%). Disease Risk Index[10] was very high in 106 (4.5%), high in 775 (33%), intermediate in 1376 (59%), and low in 77 (3.3%).

During the follow-up period, 1416 patients died and main causes of death were allo-HCT-related (n = 710) and relapse of t-MN (n = 706). Among the 710 patients without t-MN relapse, infection was the cause of death in 273 (38%) and graft versus host disease (GVHD) in 172 (24%) patients (Suppl. Table 2S). A minority of patients (3%) died from another malignancy without details whether it was the primary cancer or a second cancer including post-transplant lymphoproliferative disease.

Five-year OS and 5-year RFS were 34% (95% CI: 32-36) and 32% (95% CI: 30-34), respectively. The association between OS and disease stage was significantly different in patients with AML and with MDS (test for interaction disease × disease stage $P < 0.001$). Five-year OS was significantly better in patients with AML in CR (43% [39-46] versus 22% [17-27]), hazard ratio (HR): 0.48, 95% CI, 0.41-0.56, $P < 0.001$) while CR status at time of allo-HCT did not significantly impact outcome in MDS patients (30% [24-37] versus 29% [25-33], HR: 0.87, 95% CI, 0.73-1.04, $P = 0.13$). OS was also related to disease risk index (DRI) with 5-year OS estimated at 61% [49-74] in low risk, 39% [36-42] in intermediate risk, 26% [22-30] in high risk, and 11% [5-17] in very high risk ($P < 0.001$). Patients with normal cytogenetics (n = 397) had a better 5-year OS than patients with aberrant cytogenetics (n = 1036) (43% [38-49] versus 33% [30-36], $P < 0.001$) as well as patients who did not receive a previous autologous transplant (no autologous transplant, 37% [34-39], 1, 29% [18%-40%], 2: 25% [20-29], $P < 0.001$). OS was significantly better using a SIB donor (38% [34-42] versus 32% [30-35], $P = 0.05$) and in patients with better Karnofsky

Table 1

Results of Multivariable Analyses by (Cause-specific) Cox Proportional Hazards Models

	Overall Survival		Disease-free Survival		Relapse Incidence		Nonrelapse Mortality	
	HR (95% CI)	*P* Value[a]	HR (95% CI)	*P* Value[a]	HR (95% CI)	*P* Value[a]	HR (95% CI)	*P* Value[a]
Age (continuous, 10 y)	1.04 (0.98-1.10)	0.19	1.02 (0.97-1.08)	0.45	0.93 (0.86-1.00)	0.05	1.16 (1.06-1.26)	0.001
Performance status								
Karnofsky ≥90 (reference)	1.00		1.00		1.00		1.00	
Karnofsky <90	1.33 (1.18-1.50)	<0.001	1.26 (1.11-1.42)	<0.001	1.27 (1.08-1.50)	0.003	1.22 (1.02-1.47)	0.03
Regimen intensity								
Reduced (reference)	1.00		1.00		1.00		1.00	
Myeoloablative	1.07 (0.94-1.22)	0.28	0.98 (0.86-1.11)	0.71	0.77 (0.65-0.92)	0.004	1.29 (1.07-1.56)	0.007
Donor type								
HLA-matched sibling (reference)	1.00		1.00		1.00		1.00	
Other	1.21 (1.06-1.38)	0.004	1.10 (0.97-1.25)	0.15	0.88 (0.75-1.04)	0.13	1.48 (1.21-1.82)	<0.001
Previous auto-HCT								
None (reference)	1.00		1.00		1.00		1.00	
1 or more	1.27 (1.08-1.49)	0.004	1.19 (1.01-1.40)	0.03	1.30 (1.04-1.62)	0.02	1.06 (0.84-1.35)	0.61
t-MN category		<0.001		<0.001		<0.001		<0.001
MDS (reference)	1.00		1.00		1.00		1.00	
AML in CR	0.79 (0.69-0.90)		0.78 (0.68-0.89)		0.80 (0.67-0.95)		0.77 (0.63-0.93)	
AML not in CR	1.47 (1.24-1.75)		1.45 (1.22-1.72)		1.55 (1.23-1.96)		1.31 (1.01-1.70)	
Primary cancer		0.18		0.42		0.95		0.006
Breast cancer (reference)	1.00		1.00		1.00		1.00	
Hodgkin lymphoma	1.24 (0.92-1.68)		1.17 (0.93-1.47)		0.94 (0.69-1.27)		1.54 (1.10-2.17)	
Non-Hodgkin lymphoma	1.25 (1.00-1.57)		1.13 (0.95-1.34)		0.90 (0.71-1.13)		1.48 (1.15-1.92)	
CLL	1.18 (0.99-1.41)		1.17 (0.87-1.58)		0.93 (0.61-1.41)		1.54 (1.01-2.34)	
Plasma cell disease	1.11 (0.95-1.31)		0.96 (0.71-1.30)		0.99 (0.66-1.46)		0.91 (0.55-1.48)	
Other solid tumor	0.96 (0.70-1.31)		1.01 (0.86-1.18)		0.92 (0.75-1.14)		1.12 (0.88-1.44)	

[a]*P* values were obtained with the Wald test.

AML = acute myeloid leukemia; CI = confidence interval; CLL = chronic lymphocytic leukemia; CR = complete remission; HCT = hematopoietic cell transplant; HR = hazard ratio; MDS = myelodysplastic syndrome; t-MN = therapy-related myeloid neoplasms.

score (38 [35-41] for Karnofsky score 90 or 100 versus 28% [24-32] if score ≤80, $P < 0.01$). Of key importance, 5-year OS was impacted by the primary cancer with the best OS in patients with t-MN postbreast cancer: breast cancer (41% [37-45]), NHL (30% [26-34]), HL (29% [22-35]), ST (34% [29-38]), CLL (34% [24-44]), and PCD (32% [21-42]) ($P < 0.001$). Five-year non-relapse mortality (NRM) was higher after utilization of a non-SIB donor (34% [31-36] versus 23% [20-27], $P < 0.001$) and after MAC (33% [30-37] versus 28% [26-31], $P < 0.001$). NRM was also associated with the primary cancer with the highest NRM in t-MN post NHL (37% [32-41]) and the lowest in postbreast cancer (24% [21-28]). Five-year RFS was not impacted by the primary cancer but all other variables prognostic for OS were also predictive for RFS (univariate analysis not shown, multiple variables analysis in Table 1). Relapse incidence was higher after reduced intensity conditioning regimen (RIC) (40% [38-43] versus 34% [30-38], $P = 0.014$) and was significantly influenced by the primary type of cancer. Survival curves estimating the outcomes according to the primary cancer are shown in Figure 1. Acute GVHD and chronic GVHD incidence were not significantly different according to the primary cancer (Suppl. Table 3S and Suppl. Figure 1S).

Multiple variables Cox (cause-specific) proportional hazards models were generated to assess the impact of the primary type of cancer, adjusting for potential confounders: age, previous autologous transplantation, regimen intensity, donor type, Karnofsky score, t-MN category (AML in CR, AML not in CR, MDS). Using postbreast cancer t-MN as a reference, patients

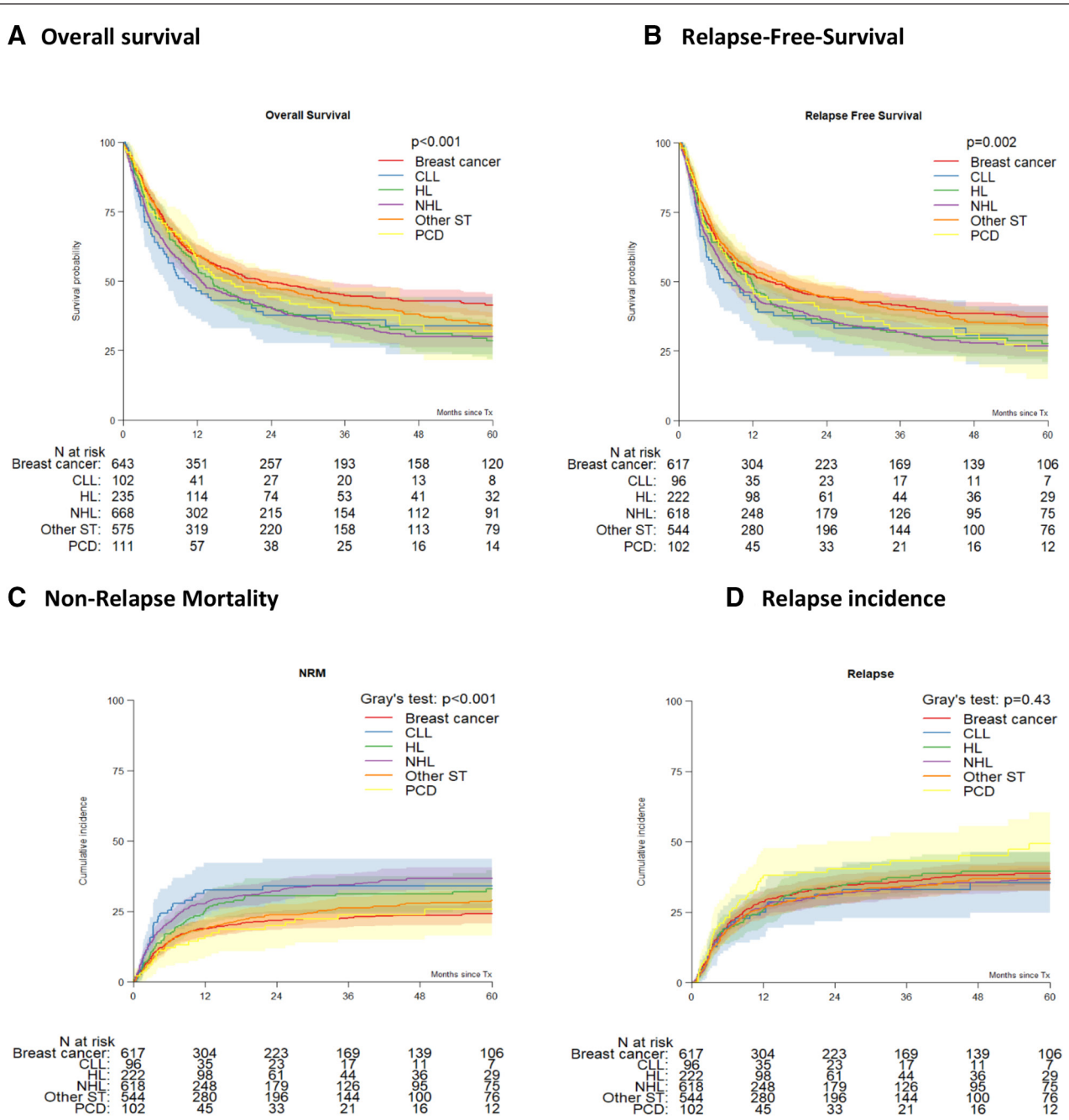

Figure 1. Outcome in patients with tMN according to the primary cancer. Overall survival (A), relapse-free survival (B), cumulative incidence of nonrelapse mortality (C), and cumulative incidence of relapse (D) according to the primary disease. CLL = chronic lymphocytic leukemia; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; PCD = plasma cell disease; ST = solid tumor.

with Hodgkin lymphoma, non-Hodgkin lymphoma or CLL had a significantly higher adjusted risk of events for NRM and a trend to a higher risk of overall mortality (Table 1). Of particular note, relapse risk for t-MN was not impacted by the primary cancer. Results from the multivariable models are shown in Table 1.

Our study, including a large number of therapy-related MDS and AML, hence confirmed that outcome, and particularly NRM, is influenced by the antecedent primary disease. Post-breast cancer t-MN had the lowest risk of NRM compared with lymphoid disorders. Unfortunately, complete molecular data were not available in the registry to analyze if these patients differ according to genetic risk profile. However, the fact that relapse risk was not impacted by the primary disease type does not support that hypothesis. We were not able to determine the reason for the higher risk of NRM, even if pretransplant chemotherapy is known to be different in patients treated for solid cancer compared with lymphoid diseases. Patients with lymphoid disease received more frequently a previous autologous transplantation which might increase the risk of NRM. However, autologous transplantation have not increased this risk in our study, it increased the risk of relapse. Furthermore, myeloma patients who mostly received an autologous transplant were not at higher risk of NRM. Previous autologous transplant could not explain the excess risk of mortality. One hypothesis is that patients treated for chronic lymphoid disease have more profound immune deficiencies than patients treated for solid cancer and this hypothesis could perhaps be supported by the high frequency of infections as causes of death in this study.

To conclude, in patients with t-MN, the primary cancer should be taken into account to adapt transplant procedures accordingly, limiting potential toxicity (myeloablative regimen) and to better prevent infection in patients with previous chronic lymphoid diseases who may be at higher risk of infection and non-relapse post-transplant mortality.

ACKNOWLEDGMENTS

The authors thank all members of the CMWP and centers which participate.

AUTHOR CONTRIBUTIONS

MR wrote the paper; JW and LCW performed statistics; MR, DPM, and IYA supervised the study; all coauthors read and validate the paper; all coauthors (except statisticians) provide patients data.

DISCLOSURES

The authors have no conflicts of interest to disclose.

REFERENCES

1. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. *Nat Rev Cancer*. 2017;17:513–527.
2. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a National Population-Based Cohort Study. *J Clin Oncol*. 2015;33:3641–3649.
3. Nilsson C, Hulegårdh E, Garelius H, et al. Secondary acute myeloid leukemia and the role of allogeneic stem cell transplantation in a population-based setting. *Biol Blood Marrow Transplant*. 2019;25:1770–1778.
4. Kröger N, Brand R, van Biezen A, et al. Risk factors for therapy-related myelodysplastic syndrome and acute myeloid leukemia treated with allogeneic stem cell transplantation. *Haematologica*. 2009;94:542–549.
5. Litzow MR, Tarima S, Pérez WS, et al. Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia. *Blood*. 2010;115:1850–1857.
6. Metheny L, Callander NS, Hall AC, et al. Allogeneic transplantation to treat therapy-related myelodysplastic syndrome and acute myelogenous leukemia in adults. *Transplant Cell Ther*. 2021;27:923.e1–923.e12.
7. Nabergoj M, Mauff K, Beelen D, et al. Allogeneic hematopoietic cell transplantation in patients with therapy-related myeloid neoplasm after breast cancer: a study of the Chronic Malignancies Working Party of the EBMT. *Bone Marrow Transplant*. 2022;57:1072–1078.
8. Sengsayadeth S, Labopin M, Boumendil A, et al. Transplant outcomes for secondary acute myeloid leukemia: acute leukemia working party of the European Society for Blood and Bone Marrow Transplantation Study. *Biol Blood Marrow Transplant*. 2018;24:1406–1414.
9. Kröger N, Eikema D-J, Köster L, et al. Impact of primary disease on outcome after allogeneic stem cell transplantation for transformed secondary acute leukaemia. *Br J Haematol*. 2019;185:725–732.
10. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the disease risk index for allogeneic stem cell transplantation. *Blood*. 2014;123:3664–3671.