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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

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We performed a registry study on therapy-related myeloid neoplasm (t-MN), both therapy-related myelodysplastic syndrome (t-MDS) and acute myeloid leukemia (t-AML) following treatment for breast cancer who underwent a first allogeneic hematopoietic cell transplant (allo-HCT). Of 252 identified female patients (median age 57 years), 77% were transplanted for t-AML and 23% for t-MDS, with a median time from breast cancer diagnosis to the diagnosis of tMN and subsequent allo-HCT of 3.7 and 4.6 years, respectively. At transplant, 191 patients were in remission for breast cancer, while 4 were not (57 missing). T-MN was in a complete remission at the time of transplant in 67% of patients. 2-year overall survival, relapse free-survival, relapse incidence and non-relapse mortality were 50%, 45%, 33%, and 22%, respectively. Multivariable analysis revealed that if the t-MN was not in CR pre-transplant, this was associated with lower OS, RFS, and a higher relapse incidence. Seventeen cases of breast cancer recurrence were recorded after a median of 2.4 years post-transplant, and relapse of primary breast cancer accounted for 7% of deaths. This study indicates that allo-HCT for t-MN following treatment for breast cancer shows encouraging transplant outcomes. The incidence of breast cancer relapse post-transplant remains a cause for concern.

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INTRODUCTION

Breast cancer represents by far the most common cancer in women, with 2.3 million cases in 2020 of a total of 9.2 million new cancer cases worldwide [1]. Apart from deaths due to cancer, an increasing number of patients and survivors will experience complications caused by treatment [2, 3], e.g., neurotoxicity, osteoporosis, impaired sexual life and fertility [4], cardiomyopathy [5], and others. Another recognized long-term complication is secondary cancer, including therapy-related myeloid neoplasms (t-MN) [6].

T-MN are recognized in the current WHO classification as a separate group of myeloid diseases which arise as a complication of chemotherapy and/or radiotherapy administrated to treat malignancies or autoimmune disease. Altogether, they account for 10–20% of all cases of myelodysplastic syndromes (MDS), acute myeloid leukemias (AML), and myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes (MDS/MPN) [7].

The median age at diagnosis of t-MN is 65 years [8], with a median time to the development of t-MDS of 4.6 years and of t-AML of 5.3 years. The highest relative risks follow chemotherapy for bone/soft tissue and testis cancers, with breast cancer having a relative risk of 3.8 [6]. In a large retrospective study performed on 20,063, patients with early-stage breast cancer treated with adjuvant therapy, the incidences of t-MN were 0.24% at 5 years

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and 0.48% at 10 years, with a median age at diagnosis of 59.1 years [9]. The higher leukemogenic effect of combined chemotherapy and radiotherapy has already been reported as has been the dose-dependent risk associated with two commonly used agents, cyclophosphamide, and melphalan [10].

The prognosis of t-MN is poorer than that of de novo counterparts due to disease-related factors such as adverse cytogenetic and molecular features as well as patient-related variables such as comorbidities, age, and side effects of prior chemotherapy [11–14]. Outcomes following conventional chemotherapy are disappointing, even in younger patients [12] and in those with good cytogenetic features [15]. Despite the encouraging results of novel treatments, e.g., venetoclax or CPX-351 [16, 17], patients with t-MN remain underrepresented in clinical trials [18], and allogeneic hematopoietic cell transplantation (allo-HCT) is therefore considered to be the only curative treatment [14, 19, 20]. Of note, a prior cancer history is equally recognized as a negative prognostic factor for non-relapse mortality after allo-HCT in the commonly used HCT-CI score [21].

Given the advances in breast cancer screening and treatment, the survival rates for breast cancer increased progressively up to 60–99% at 5 years, depending on several factors [22–24]. As a consequence, the number of cancer survivors is constantly increasing, with more than 16.9 million US inhabitants in 2019 having a history of cancer [2]. On the same basis, t-MN have increased in the recent period [6, 8].

In this retrospective registry-based study, we focused on patients who developed t-MN following treatment for breast cancer, with a view to gathering more robust data on outcomes during and after allo-HCT in this well-defined cohort.

MATERIALS AND METHODS

We conducted a retrospective, multicenter, registry-based study on behalf of the Chronic Malignancies Working Party of EBMT. The EBMT is a non-profit scientific society of more than 600 transplant centers, mostly in Europe, that report on all transplants each year. All data is stored in a central database. Patients or their legal guardians provide informed consent authorizing the use of their personal information for research purposes according to the ethical principles of the Declaration of Helsinki. Once the patient and their centers were identified in the EBMT registry, a targeted survey was created, to collect more data regarding hematological diseases and breast cancer diagnoses and characteristics, treatment, and subsequent relapse, if any, following allo-HCT. The study was approved by CMWP of the EBMT.

Eligibility criteria

Eligible for inclusion were all adult patients (≥18 years) who underwent a first allo-HCT between 2006 and 2016 for a t-MDS or t-AML secondary to breast cancer treatment with radiotherapy, chemotherapy, or both. There were no restrictions relating to the conditioning regimen or the type of donor.

Endpoints

After the characterization of the patients undergoing allo-HCT, the primary endpoint was the evaluation of the impact of analyzed variables on transplant outcomes, including overall survival (OS), relapse-free survival (RFS), non-relapse mortality (NRM) and relapse incidence (RI). Secondary endpoints were acute graft-versus-host-disease (aGVHD), chronic GVHD (cGVHD), incidence of graft failure, incidence of relapse of the primary breast cancer, and causes of death. All outcomes were measured from the day of the allo-HCT to the date of the event of interest, i.e., death, relapse, GVHD, whichever occurred first. In the case of no event, patients were censored at the date of the last follow-up visit.

Statistical analysis

Continuous variables were illustrated as median values and interquartile range (IQR: Q1–Q3) and compared using Wilcoxon signed-rank test; categorical variables were summarized as counts and percentages and compared using the Chi-Squared or Fisher's Exact test. Median follow-up was calculated as per the reverse Kaplan-Meier method. OS and RFS were assessed using the Kaplan Meier method with log-rank tests for univariate analysis of survival; multivariable analyses adjusted for variables differing significantly or variables that were clinically relevant were performed using the Cox proportional hazards regression model. Competing risk outcomes (NRM, RI, aGVHD, cGVHD) were assessed using cumulative incidence to accommodate competing risks, together with Gray's test and cause-specific Cox proportional hazards models, with only death considered as a competing event among analyzed outcomes. All statistical tests were two-sided, and $P < 0.05$ was considered significant. Analyses were performed using R version 3.6.3 (R Foundation, USA), using the packages survival (version 3.1.12), cmprsk (version 2.2.9), and prodlim (version 2019.11.13).

RESULTS

Study cohort

In the EBMT registry, a total of 252 female patients fulfilled the criteria and were included in the final analysis. The median age at transplantation was 57 years (IQR 49.6–62.7), and the median time from the breast cancer diagnosis to t-MN diagnosis and subsequent allo-HCT were 3.7 (IQR 2.2–6.8) and 4.6 (IQR 2.8–8) years, respectively. T-AML was the indication for allo-HCT in 77% of cases. Regarding t-MN, an abnormal karyotype at diagnosis was reported in 178 (77%) patients, of which 28 (12%) were complex. A total of 88 (72%) and 26 (21%) patients received either intensive chemotherapy or hypomethylating agents prior to allo-HCT, respectively, while data were missing for 129 patients. At transplant, 169 (67%) patients were in complete remission (CR) whereas 73 (29%) had either stable or progressive disease; nine (4%) proceeded to allo-HCT without any prior treatment. A Karnofsky Performance Score (KPS) of <90 was recorded in 67 patients (29%, 21 missing) while 71 (49%) patients presented with at least one comorbidity other than the primary malignancy (missing values for 106 patients). Conditioning regimens were reduced-intensity (RIC) in 152 (61%) and myeloablative (MAC) in 99 (39%) patients, respectively, and in vivo T-cell depletion was performed in 138 (55%) cases. Mobilized peripheral blood was the stem cell source in 225 (89%) patients. Ninety-nine (39%) patients had a MRD.

With regards to the breast cancer diagnosis, eight (5%) patients presented with metastatic disease and 15 (15%) had triple-negative breast cancer (missing data for 90 patients); 163 (86%) received chemotherapy, 172 (88%) radiotherapy, and 130 (73%) both. For breast cancer, at transplant, 93% of patients were deemed to be in first CR, and an additional 5% were in second CR or later; data on remission status were missing for 57 patients. Further patients' and donors' characteristics and transplantation details are shown in Tables 1 and 2. Treatments received for t-MN are illustrated in Supplementary Table S1, while data on cytogenetics are shown in detail in Supplementary Tables S2 and S3.

OS and relapse-free survival

After a median follow-up from transplant of 20 months (IQR 5–60), the 2-year estimated OS and RFS were 50% [95% confidence interval (CI): 44–56, Fig. 1] and 45% (95% CI: 39–52, Fig. 2), respectively. In univariate analysis for OS, a worse outcome was observed in (1) patients presenting with a KPS < 90 pretransplant [43% (95% CI: 31–55) for KPS < 90, 55% (47–63) for KPS ≥ 90, $p = 0.05$], (2) in those transplanted within 2 years of the t-MN diagnosis [48% (95% CI: 42–55) for ≤2 years, 82% (59-100) for >2 years, $p = 0.037$], and (3) in those not in CR (t-MN) at transplant [57% (95% CI: 49–64) for CR, 56% (23–88) for untreated, 34% (23–45) for not in CR, $p = 0.002$]. In multivariable analysis for OS, the adverse impact of being transplanted with active disease was confirmed [HR 1.76 (95%CI: 1.2–2.59, $p = 0.004$) over being transplanted in CR].

When performing univariate analysis for RFS, adverse factors included (1) t-MN not being in remission pre-allo-HCT [52% for CR

Table 1. Baseline characteristics of 252 patients undergoing an allo-HCT for t-MN secondary to breast cancer treatment at the time of allo-HCT.

Median age at allo-HCT, years (IQR)	**57 (49.6–62.7)**
≤55 years, *n* (%)	112 (44)
>55 years, *n* (%)	140 (56)
Median follow-up, months (IQR)	20 (5–60)
Year of allo-HCT, median (IQR)	2012 (2009–2014)
Indication for allo-HCT, *n* (%)	
t-AML	193 (77)
t-MDS	59 (23)
Interval from breast cancer diagnosis to t-MN diagnosis, years, median (IQR)	3.7 (2.2–6.8)
Interval from breast cancer diagnosis to allo-HCT, years, median (IQR)	4.6 (2.8 to –8)
≤2 years, *n* (%)	31 (12)
>2 years, *n* (%)	221 (88)
Karyotype, *n* (%)	
Abnormal	178 (77)
Balanced translocation	49 (21)
Unbalanced translocation	46 (20)
Complex	28 (12)
Chromosomal numerical abnormalities	11 (5)
Not specified	44 (19)
Normal	54 (23)
Missing data	20
t-MN status at allo-HCT, *n* (%)	
CR	169 (67)
t-AML	144 (57)
t-MDS	25 (10)
Not CR	73 (29)
t-AML	46 (18)
t-MDS	27 (11)
Untreated	9 (4)
t-AML	6 (3)
t-MDS	3 (1)
Missing data	1
Breast cancer status at allo-HCT, *n* (%)	
CR1	182 (93)
CR > 1	9 (5)
Not in CR	4 (2)
Missing data	57
Karnofsky status, *n* (%)	
<90	67 (29)
≥90	164 (71)
Missing data	21
Comorbidities, other than breast cancer (considered in HCT-CI), *n* (%)	
0	75 (51)
1	41 (28)
≥2	30 (21)
Missing data	106
Donor, *n* (%)	
MRD	99 (39)
MUD	76 (30)
MMRD	8 (3)
MMUD	47 (19)
Unrelated, matching unknown	22 (9)
Stem cell source, *n* (%)	
Peripheral blood	225 (89)
Bone marrow	19 (8)
Cord blood/CB + PB	8 (3)
Conditioning intensity, *n* (%)	
MAC	99 (39)
RIC	152 (61)
Missing data	1
ATG, *n* (%)	
Yes	138 (55)
No	111 (45)
Missing data	3
TBI, *n* (%)	
Yes	45 (18)
No	203 (82)
Missing data	4
DLI treatment after allo-HCT, *n* (%)	
Yes	31 (14)
No	194 (86)
Missing data	27

IQR interquartile range, *allo-HCT* allogeneic hematopoietic cell transplantation, *DLI* donor lymphocyte infusion, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *ATG* anti-thymocyte globulin, *TBI* total body irradiation.

(95% CI: 44–59), 44% for untreated (12–77), 31% (20–42) for not in CR, $p = 0.002$] and (2) allo-HCT within 2 years of t-MN diagnosis [43% (95% CI: 37–50) for ≤2 years, 90% (71–100) for >2 years, $p = 0.01$]. Multivariable analyses for RFS confirmed that an uncontrolled hematological disease was associated with inferior outcomes [HR 1.74 (95%CI: 1.19–2.54, $p = 0.005$) over being transplanted in CR]. Univariate analyses for OS and RFS are shown in Supplementary Table S4. Multivariable analyses are illustrated in Table 3.

Non-relapse mortality and relapse incidence

Two-year RI and NRM were 33% (95%CI: 27–39, Fig. 3) and 22% (17–27, Fig. 4), respectively. In univariate analysis, an abnormal karyotype at diagnosis was significantly associated with a higher relapse rate compared to a normal karyotype [37 (95% CI: 30–45) vs 21% (10-32%), $p = 0.02$], as did an uncontrolled t-MN pre-transplant [27% (95% CI: 20–34) for CR, 33% (3–64) for untreated, 47% (35–59) for not in CR, $p < 0.001$]. Patients who had radiotherapy treatment for their breast cancers experienced a higher relapse rate compared to those who did not [35 (95% CI: 28–43) vs 17% (2–33), $p = 0.04$], though they had a lower NRM [18 (95% CI: 12–24) vs 38% for no radiotherapy (19–58), $p = 0.02$]. Univariate analyses for RI and NRM are shown in detail in Supplementary Table S2.

In multivariable analysis for RI (Table 3), the t-MN not being in CR remained a significant predictive factor [HR 2.32 (95% CI: 1.43–3.76), $p = 0.001$) compared to being transplanted in CR]. Due to an insufficient number of events, previous treatment with radiotherapy could not be assessed in multivariable analyses for RI

Table 2. Baseline Breast cancer characteristics at diagnosis of 252 patients.

TMN classification, Primary tumor (T), *n* (%)	
T1	75 (45)
T2	62 (38)
T3	22 (13)
T4	7 (4)
Missing data	85
Regional lymph nodes (*N*), *n* (%)	
NX	3 (2)
N0	72 (44)
N1	67 (41)
N2	13 (8)
N3	10 (6)
Missing	87
Distant metastasis (M), *n* (%)	
MX	9 (6)
M0	145 (89)
M1	8 (5)
Missing	90
Hormonal Status	
Negative	25 (18)
Positive	112 (82)
Missing	115
Estrogen Receptor (ER) status	
Negative	30 (22)
Positive	108 (78)
Missing	114
Progesterone Receptor (PgR) status	
Negative	46 (36)
Positive	81 (64)
Missing	125
HER2/neu (c-erb-B2) receptor status	
Negative	84 (70)
Positive	36 (30)
Missing	132
Triple negative, *n* (%)	
Yes	15 (15)
No	87 (85)
Missing	150
Radiotherapy, *n* (%)	
Yes	172 (88)
No	24 (12)
Missing	56
Chemotherapy, *n* (%)	
Yes	164 (87)
No	25 (13)
Missing	63
Chemo- and radiotherapy, *n* (%)	
Yes	130 (72)
No	50 (28)
Missing	73

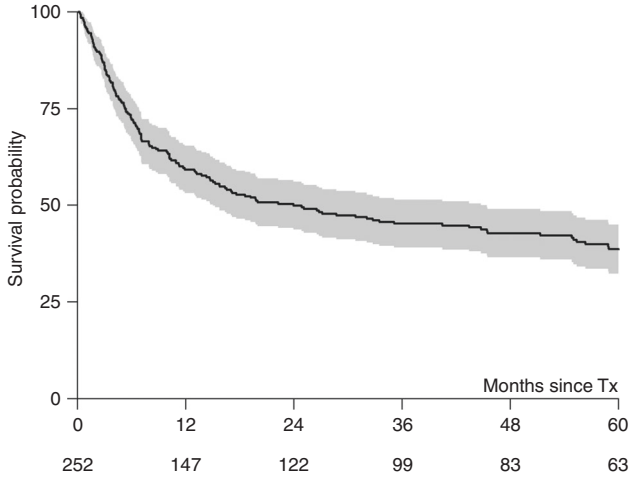

Fig. 1 Overall survival (OS) after transplant within the entire cohort. Gray area denotes 95% confidence interval, CI, over time.

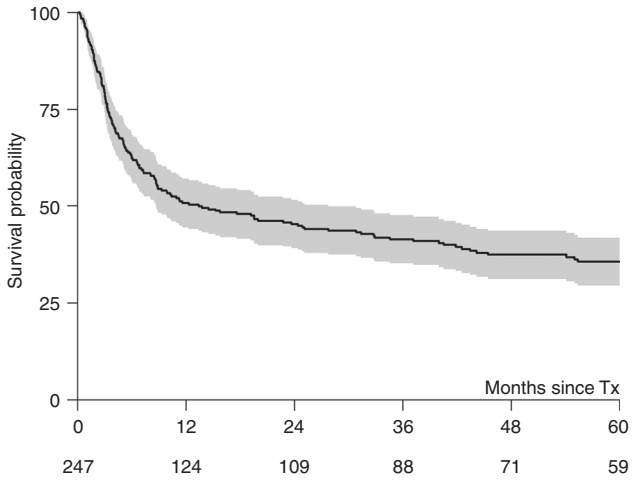

Fig. 2 Relapse-free survival (RFS) after transplant within the entire cohort. Gray area denotes 95% confidence interval, CI, over time.

and NRM. For NRM none of the factors explored were significant in multivariable analyses.

Acute and chronic graft versus host disease

The cumulative incidence of all grades (II–IV) of aGvHD in the first three months post-transplant was 28% (95% CI: 22–33, Supplementary Fig. S1). No significant factor could be found in univariate analysis for aGVHD. The 2-year incidence of all grades of cGVHD and extensive cGVHD were 41% (95% CI: 35–47, Supplementary Fig. S2) and 22% (17–27, Supplementary Fig. S2), respectively. A higher incidence of all grades of cGVHD was observed in (1) patients with t-MDS [37% (95% CI: 30–44%) for AML vs 55% (41–68) for MDS, $p = 0.02$] and in (2) those who received a MAC [49% (95% CI: 39–60) for MAC vs 36% (28–44) for RIC, $p = 0.03$] without any significant impact on extensive cGVHD. A higher incidence of all-grade and extensive cGVHD was observed in untreated patients [for all grade cGVHD: 45% (95% CI: 37–52) for CR, 62% (29–96) for untreated, 30% (19–41) for not in CR, $p = 0.02$; for extensive cGVHD 23% (16–29) for CR, 50% (15–85) for untreated, 16% (7–25) for not in CR, $p = 0.01$]. These findings were subsequently either not confirmed in the multivariable

Table 3. Multivariable analysis of risk factors for different outcomes after allo-HCT for t-MN secondary to breast cancer treatment.

Variables	OS		RFS		Relapse		NRM		aGVHD (grades 2–4)		cGVHD	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age												
≤55 years	Reference											
>55 years	1.24 (0.85–1.8)	0.27	1.14 (0.79–1.64)	0.489	0.97 (0.61–.56)	0.906	1.4 (0.78–2.5)	0.255	0.96 (0.57–1.63)	0.892	1.16 (0.77–1.75)	0.488
Karnofsky status												
<90	Reference											
≥90	0.71 (0.49–1.03)	0.075	0.71 (0.49–1.03)	0.075	0.84 (0.52–1.38)	0.502	0.58 (0.33–1.02)	0.057	0.85 (0.48–1.48)	0.555	0.89 (0.57–1.4)	0.624
Karyotype												
Normal	Reference											
Abnormal	0.95 (0.62–1.45)	0.808	1.08 (0.71–1.65)	0.716	1.5 (0.82–2.75)	0.187	0.75 (0.41–1.37)	0.351	0.94 (0.52–1.7)	0.837	1.01 (0.63–1.62)	0.975
Hematological stage at allo-HCT												
CR	Reference											
Untreated	0.96 (0.34–2.69)	0.94	0.88 (0.32–2.46)	0.807	1.23 (0.37–4.11)	0.732	0.48 (0.06–3.63)	0.48	0.47 (0.06–3.51)	0.463	2.99 (1.16–7.74)	0.024
Not in CR	1.76 (1.2–2.59)	0.004	1.74 (1.19−2.54)	0.005	2.32 (1.43–3.76)	0.001	1.11 (0.59–2.11)	0.744	1.42 (0.82–2.46)	0.211	1.07 (0.66–1.75)	0.783

OS Overall survival, *RFS* Relapse free survival, *NRM* Non-relapse mortality, *HR* hazard ratio, *CI* confidence interval.

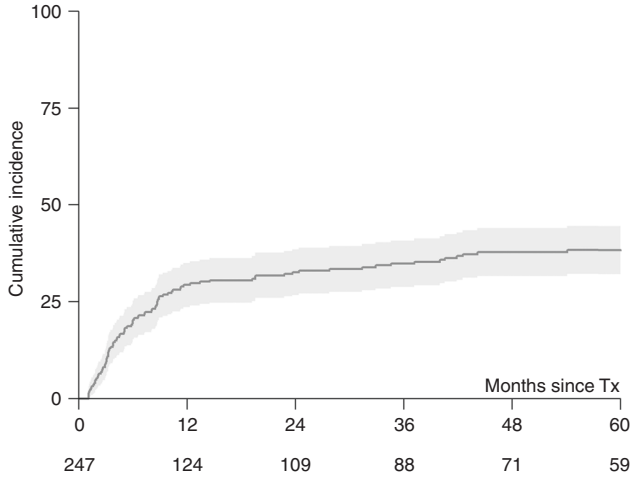

Fig. 3 Cumulative Relapse incidence (RI) after transplant within the entire cohort. Gray area denotes 95% confidence interval, CI, over time.

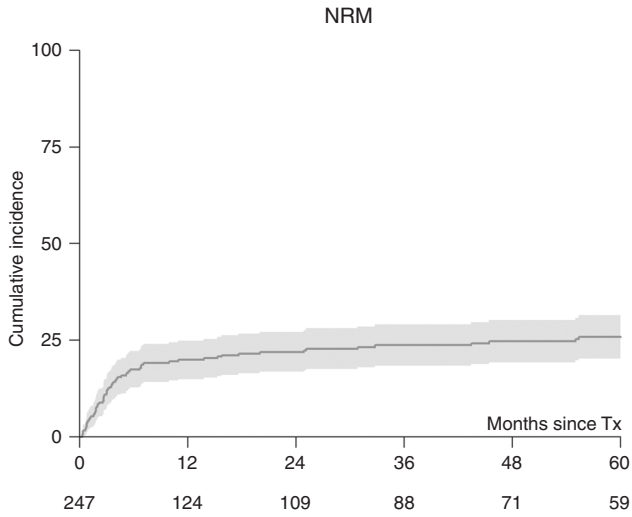

Fig. 4 Cumulative incidence of Non-relapse mortality (NRM) after transplant within the entire cohort. Gray area denotes 95% confidence interval, CI, over time.

model or not explored due to an insufficient number of events (Table 3). Univariate analysis for aGVHD and cGVHD are illustrated in Supplementary Table S5.

Engraftment and long-term complications

Engraftment was achieved in 230 (94%) patients, whereas ten (4%) and two (1%) experienced primary or secondary graft failure, respectively.

Overall, 17 (9%) cases of breast cancer recurrence were recorded at a median interval from allo-HCT of 2.4 years (IQR 0.6–4.4), of which 13 were invasive. Curative treatment was given to seven patients, while for five patients, a palliative approach was adopted.

At the end of follow-up, 159 (63%) patients had deceased. The principal cause of death was relapse of the t-MN in 54 patients (36%), followed by infection in 42 (28%) and GVHD in 24 patients (16%). Finally, ten (7%) deaths were due to relapse of primary breast cancer. Univariate analysis for breast cancer recurrence are shown in Supplementary Table S6.

Subgroup analysis for t-AML and t-MDS

Patients with t-MDS showed a 2-year OS, PFS, NRM, and relapse incidence of 61% (95% CI: 48–73), 56% (43–69), 21% (10–32), and 23% (12–34), respectively. In univariate analysis, radiotherapy for breast cancer was associated with a higher NRM ($p = 0.03$), while an active disease exhibited a higher risk of relapse ($p = 0.05$).

In t-AML, patients in CR at the time of allo-HCT presented favorable outcomes compared to those not in CR (2-year OS 54% (95% CI: 46-62) vs 22% (10–35), $p < 0.001$; PFS 49% (40–57) vs 19% (7–31), $p < 0.001$; relapse 30% (23–38) vs 54% (39–69), $p < 0.001$; NRM 21% (14–28) vs 28% (14–41), $p = 0.4$). In those in CR, an adverse cytogenetic risk was associated with a higher relapse risk ($p < 0.001$). For patients not in CR at the time of allo-HCT, a poor KPS and higher age were associated with worse NRM ($p = 0.04$) and relapse incidence ($p = 0.01$), respectively. Univariate analysis are shown in Supplementary Table S7.

DISCUSSION

Although there have been several reports on patient outcomes following allo-HCT for t-MN, none have focused exclusively on t-MN following treatment for breast cancer, nor have they reported on the incidence of relapse of breast cancer post-transplant.

The heterogeneity of t-MN may yield different results when investigating the role of allo-HCT. For example, Michelis et al. found that patients with de novo and secondary AML had comparable rates of OS, RFS, NRM, and RI [19]. In contrast, a recent EBMT ALWP study found poorer outcomes in t-AML when compared to de novo AML with regard to all explored variables independent of conditioning intensity or cytogenetic risk [25]. In a German-Austrian study, younger patients (≤60 years) with t-AML had a higher NRM rate post-allo-HCT whereas older patients had a significant higher RI, both resulting in inferior OS and RFS in tMN compared to de novo AML [12].

In our study, focused on 252 female transplant recipients, the median time from diagnosis of breast cancer to the subsequent allo-HCT was 4.6 years, with only 31 (12.3%) patients being transplanted within 2 years. This may reflect both the generally delayed occurrence of t-MN following treatment [6] and the frequent choice of physicians to wait at least 2 years after the diagnosis of breast cancer prior to proceeding with an allo-HCT for the t-MN. This can result in a degree of selection bias as patients who have survived more than 2 years are likely to have had less aggressive breast cancer.

Our outcomes are comparable to those of the afore-mentioned studies with 2-year OS, RFS, relapse incidence, and NRM of 50%, 45%, 33%, and 22%, respectively, not significantly different between t-MDS and t-AML similarly as recently reported by the CIBMTR in a study conducted on 1531 t-MN [26]. The expected prognostic factors such as poor performance status and the t-MN not being in remission pre-transplant correlated with poorer outcomes with regard to OS, RFS, and relapse incidence, especially for t-AML, while the negative impact of having an abnormal karyotype at diagnosis was potentially mitigated by a lack of disease control at allo-HCT, as previously described [27]. Of note, in our analysis, an older age at allo-HCT was not associated with an inferior outcome as reported by Kröger et al. [28]. The conditioning regimen intensity did not show any impact on outcomes, in contrast to other studies where either MAC or RIC was found to be associated with poorer prognosis in the setting t-AML arising follow prior lymphoid malignancy [29] and follow solid cancer [30].

Of primary cancer-related variables included in the analysis, only radiotherapy as part of the prior therapy for breast cancer was found to be significant in univariate analysis in predicting a lower NRM and a higher relapse incidence. Unfortunately, firm conclusions regarding the effect of breast cancer radiotherapy could not be drawn because of lack of details on treatment modalities, absence of association with other risk factor and small patient numbers (no radiotherapy in 25 subjects). Of note, no difference was recorded when stratifying patient outcomes based on the time between diagnosis of the breast cancer and allo-HCT (more as opposed to less than 2 years), reinforcing the importance of a thorough selection process and consultation with the oncologist. Remarkably, previous exposure to anthracyclines was not associated with worse outcomes, even in those who received radiotherapy.

Seventeen (9%) cases of breast cancer recurrence were reported at a median of 2.4 years post-allo-HCT. A curative approach was only possible in seven cases though no further details were available. Nevertheless, relapse of the primary malignancy accounted for a significant number of deaths in our cohort (7%). Interestingly, the time between the breast cancer diagnosis and the transplant did not emerge as a significant factor for breast cancer recurrence. As expected, patients transplanted with active disease progressed inexorably. The small number of patients transplanted with progressive breast cancer could not allow us to investigate a potential graft- versus-breast cancer effect. Due to different patterns of relapse among breast cancer subtypes [31], we acknowledge that a longer follow-up would be needed to catch a higher number of recurrencies and explore the impact of additional therapies for breast cancer.

Limitations

to this study are those of a retrospective study: we did not have access to complete cytogenetic and molecular data. Besides, data on minimal residual disease were not available for any cohort patient. In addition, treatment approaches have evolved over these years, with an unpredictable effect on patient outcomes.

Nevertheless, the strength of the current analysis is that our study specifically addresses t-MN secondary to breast cancer treatment, and we confirmed that allo-HCT remains a valid approach in this disease despite the higher than expected (for de novo disease) incidence of complications. Despite the retrospective nature of this study, we would like to draw attention to the non-negligible rate of primary cancer relapse, a potential source of additional harm for these patients and a potentially avoidable cause of death. A multi-disciplinary collaboration between the treating hematologist and oncologist is therefore crucial when a patient is referred for an allo-HCT, especially in terms of patient selection. Moreover, it appears of utmost importance that an adequate follow-up program should be put in place for those patients with a prior history of breast cancer who undergo an allo-HCT independently of the time elapsed from the primary cancer treatment.

In summary, our findings reinforce the need for oncologists and hematologists to intensify collaboration in the co-ordinated care of cancer survivors undergoing allo-HCT, thereby allowing for the refinement of patient selection criteria and post-transplant care.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

MN and MR designed study, interpreted the data, and wrote the first draft of manuscript. KM analyzed data and interpreted results. All authors contributed to writing the manuscript and approved the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

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