

RESEARCH ARTICLE

The role of allogeneic stem cell transplantation in acute myeloid leukemia with translocation t(8;16)(p11;p13)

Ann-Kristin Schmäler^{1,2}  | Myriam Labopin³ | Jurjen Versluis⁴ |
 Maria Pilar Gallego Hernanz⁵ | Matthias Eder⁶ | Peter von dem Borne⁷ |
 Gerard Socié⁸ | Patrice Chevallier⁹  | Edouard Forcade¹⁰ | Andreas Neubauer¹¹ |
 Frédéric Baron¹² | Ali Bazarbachi¹³  | Gesine Bug¹⁴  | Arnon Nagler¹⁵  |
 Christoph Schmid^{1,2} | Jordi Esteve¹⁶ | Mohamad Mohty^{3,17} | Fabio Ciceri¹⁸

¹Department of Hematology and Oncology, Augsburg University Hospital and Medical Faculty, Comprehensive Cancer Center Augsburg, Augsburg, Germany

²Bavarian Cancer Research Center (BZKF), Augsburg, Germany

³EBMT Paris Study Office, Paris, France

⁴Erasmus University Medical Center Cancer Institute, Rotterdam, The Netherlands

⁵Hematology Department, CHU de Poitiers, Poitiers, France

⁶Department of Stem Cell Transplantation, Hannover Medical School, Hannover, Germany

⁷Leiden University Hospital, BMT Centre Leiden, Leiden, The Netherlands

⁸Saint-Louis Hospital, BMT Unit, Paris, France

⁹CHU Nantes, Nantes, France

¹⁰CHU Bordeaux, Hôpital Haut-Leveque, Pessac, France

¹¹Clinic for Hematology, Oncology, Immunology, and Carreras Leukemia Center, Philipps University Marburg, Marburg, Germany

¹²CHU and University of Liege, Liege, Belgium

¹³Bone Marrow Transplantation Program, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

¹⁴Department for Hematology and Oncology, University Hospital Frankfurt, Frankfurt, Germany

¹⁵Hematology and Bone Marrow Transplantation Division, Chaim Sheba Medical Center, Tel Aviv University, Ramat Gan, Israel

¹⁶Hematology Department, Hospital Clinic Barcelona, IDIBAPS, Barcelona, Spain

¹⁷Department of Haematology, Saint Antoine Hospital, Paris, France

¹⁸IRCCS Ospedale San Raffaele, Hematology and BMT, University Vita-Salute San Raffaele, Milan, Italy

Correspondence

Christoph Schmid, Department of Hematology and Oncology, Augsburg University Hospital and Medical Faculty, Comprehensive Cancer Center Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany.
 Email: christoph.schmid@uk-augsburg.de

Abstract

Acute myeloid leukemia (AML) with translocation t(8;16)(p11;p13) represents a rare entity that has been categorized as a disease-defining recurring cytogenetic abnormality with adverse risk in the 2022 European LeukemiaNet classification. This rating was mainly based on a retrospective analysis comprising patients from several large clinical trials, which, however, included only 21 patients treated with allogeneic stem cell transplantation (alloSCT). Therefore, the European Society for Blood and Marrow Transplantation performed a registry study on a larger cohort to evaluate the role of alloSCT in t(8;16) AML. Sixty transplant recipients

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with t(8;16) AML were identified. Two-year overall and leukemia-free survival (OS/LFS) was 43/39%. Patients transplanted in first complete remission (CR1, $n = 44$) achieved a 2-year OS/LFS of 48%/48%. Following alloSCT in CR1, the multivariable analysis identified a complex karyotype (CK) as a major risk factor for relapse (HR 4.17, $p = .016$), lower LFS (HR 3.38, $p = .01$), and lower OS (HR 3.08, $p = .017$). Two-year OS/LFS of patients with CK was 19%/19%, in contrast to 67%/67% in patients with t(8;16) outside a CK. Other factors for inferior outcomes were older age and secondary AML. In summary, alloSCT could mitigate the adverse risk of patients with t(8;16) AML not harboring a CK, particularly when performed in CR1.

1 | INTRODUCTION

Translocation (8;16)(p11;p13) is a rare abnormality in acute myeloid leukemia (AML) with female preponderance, occurring more frequently in secondary AML (sAML), and especially in therapy-related (tAML) following exposure to topoisomerase-2 inhibitors.^{1,2} Clinically, t(8;16) AML is associated with disseminated intravascular coagulation, high risk of bleeding, extramedullary involvement, and hemophagocytosis.^{1,3} The translocation leads to the fusion of acetyltransferase *KAT6A* (also known as *MOZ* or *MYST3*) and *CREB* binding protein (*CREBBP*) genes, both involved in hematopoiesis.⁴ Moreover, AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* is an entity with a unique gene expression, including a characteristic microRNA profile.⁵

In the 2022 genetic risk classification by the European LeukemiaNet (ELN), t(8;16) was classified as a disease defining recurring genetic abnormality and was newly included in the adverse risk group.⁶ This genetic risk stratification was mainly based on a recent report, which included 59 patients with AML with t(8;16) from several large trial groups, thereby representing the largest cohort studied so far.⁷ Five-year overall survival (OS) was 17% for the entire cohort and 38% among 15 patients undergoing allogeneic stem cell transplantation (alloSCT) in first complete remission (CR1). Despite these low numbers, post-remission treatment with alloSCT in CR1 was associated with improved OS in multivariable analysis. Further publications containing even fewer patients seemed to confirm the unfavorable prognosis of AML with t(8;16).^{8–11} In the recent WHO classification,¹² t(8;16) was not mentioned as disease-defining aberration but may be included in the subgroup of AML with other defined genetic alterations, which might constitute distinct AML subtypes in the future.

To validate the role of alloSCT in a larger cohort of patients with t(8;16) AML, the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) performed a retrospective registry analysis, including all consecutive patients with known t(8;16) that had received an alloSCT between 2000 and 2021.

2 | METHODS

2.1 | Study design

Data were extracted from the EBMT registry, which comprises more than 600 transplant centers providing reports and annual follow-up on all consecutive stem cell transplantations. Audits are routinely performed to determine the accuracy of the data. Since 1990, patients have provided informed consent, authorizing the use of their personal information for research purposes. The study was approved by the general assembly and review board of the ALWP and complied with country-specific regulatory requirements. All consecutive patients ≥ 18 years receiving alloSCT for AML reported to harbor t(8;16) between 2000 and 2021 were included, considering all types of donors, conditioning regimens, and disease stages at the time of alloSCT. Variables of interest included de novo/secondary AML, cytogenetic risk group according to the ELN 2017 classification (molecular aberrations limited to FMS-like tyrosine kinase-3 (*FLT3*) ITD and nucleophosmin 1 (*NPM1*) mutation), disease status at alloSCT, patient and donor gender, age and cytomegalovirus (CMV) serostatus, Karnofsky performance status (KPS), hematopoietic cell transplantation-specific comorbidity index (HCT-CI), year of transplant, median time from diagnosis to alloSCT, graft source, donor type, female donor to male recipient combination, conditioning regimen, use of myeloablative or reduced intensity conditioning (MAC or RIC), in vivo or in vitro T-cell depletion (TCD) or use of post-transplant cyclophosphamide (PTCY), and graft-versus-host disease (GVHD) prophylaxis. Analyzed outcome variables comprised overall survival, leukemia-free survival (LFS), cumulative incidence of relapse (RI), non-relapse mortality (NRM), acute and chronic GVHD, and GVHD-free/relapse-free survival (GRFS).

2.2 | Definitions

Complete remission (CR) and relapse were defined as recommended, as were genetic risk categories and CK.⁶ OS was defined as the

TABLE 1 Patient, disease, and transplant characteristics.

		Entire cohort N = 60	CR1 patients N = 44
Follow-up (months)	Median [IQR]	72.34 [34.54–96.07]	72.34 [26.75–96.07]
Patient age (years)	Median (min–max) [IQR]	46.3 (18–71.7) [32.6–57.8]	47.5 (18–71.7) [32.2–56.6]
Patient sex	Female	44 (73.3%)	34 (77.3%)
	Male	16 (26.7%)	10 (22.7%)
Secondary AML	No	37 (61.7%)	22 (50%)
	Yes	23 (38.3%)	22 (50%)
Cytogenetic risk (ELN 2017)	Intermediate	31 (51.7%)	24 (54.5%)
	Adverse	29 (48.3%)	20 (45.5%)
Complex karyotype (≥3 abnormalities)	Not CK	34 (56.7%)	27 (61.4%)
	CK	26 (43.3%)	17 (38.6%)
FLT3	FLT3-wt	22 (88%)	18 (90%)
	FLT3-ITD	3 (12%)	2 (10%)
	Missing	35	24
NPM1	NPM1 absent	23 (95.8%)	19 (100%)
	NPM1 present	1 (4.2%)	
	Missing	36	25
HCT-CI	HCT-CI = 0	21 (42.9%)	11 (29.7%)
	HCT-CI = 1 or 2	5 (10.2%)	5 (13.5%)
	HCT-CI ≥3	23 (46.9%)	21 (56.8%)
	Missing	11	7
Karnofsky Performance Status	<80%	1 (1.8%)	1 (2.4%)
	≥80%	54 (98.2%)	40 (97.6%)
	Missing	5	3
Year of transplant	Median (min–max)	2016 (2002–2022)	2016 (2002–2022)
Period of transplant	2000–2004	3 (5%)	2 (4.5%)
	2005–2009	11 (18.3%)	7 (15.9%)
	2010–2014	9 (15%)	8 (18.2%)
	2015–2021	37 (61.7%)	27 (61.4%)
Interval between diagnosis and transplantation (mo)	Median [IQR] (range)	4.6 [3.8–6.2] (2.3–15.5)	4.4 [3.6–5.9] (2.3–12)
Donor type	MRD	20 (33.3%)	15 (34.1%)
	URD	32 (53.3%)	24 (54.5%)
	Haplo	4 (6.7%)	2 (4.5%)
	CBT	4 (6.7%)	3 (6.8%)
Disease status at transplantation	CR1	44 (73.3%)	44 (100%)
	CR2	4 (6.7%)	-
	Refractory disease	4 (6.7%)	-
	First relapse	8 (13.3%)	-
Donor sex	Female	19 (31.7%)	14 (31.8%)
	Male	41 (68.3%)	30 (68.2%)
Female donor to male recipient at alloSCT	No	53 (88.3%)	40 (90.9%)
	Yes	7 (11.7%)	4 (9.1%)
CMV status patient	Negative	21 (36.2%)	16 (37.2%)
	Positive	37 (63.8%)	27 (62.8%)
	Missing	2	1

(Continues)

TABLE 1 (Continued)

		Entire cohort N = 60	CR1 patients N = 44
CMV status donor	Negative	28 (49.1%)	20 (47.6%)
	Positive	29 (50.9%)	22 (52.4%)
	Missing	3	2
Cell source	BM	5 (8.3%)	5 (11.4%)
	PB	51 (85%)	36 (81.8%)
	CB	4 (6.7%)	3 (6.8%)
Conditioning	MAC	28 (46.7%)	23 (52.3%)
	RIC	32 (53.3%)	21 (47.7%)
Post-transplant cyclophosphamide	No	52 (91.2%)	39 (92.9%)
	Yes	5 (8.8%)	3 (7.1%)
	Missing	3	2
In-vivo T cell depletion	No	22 (37.9%)	13 (30.2%)
	Yes	36 (62.1%)	30 (69.8%)
	Missing	2	1

Abbreviations: alloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; BM, bone marrow; CB, cord blood; CBT, cord blood transfusion; CK, complex karyotype; CMV, cytomegalovirus; CR1, first complete remission; CR2+, second or later complete remission; ELN, European LeukemiaNet; FLT3, fms-related receptor tyrosine kinase 3; Haplo, haploidentical donor; HCT-CI, hematopoietic cell transplantation–specific comorbidity index; IQR, interquartile range; ITD, internal tandem duplication; MAC, myeloablative conditioning; max, maximum; min, minimum; mo, months; MRD, matched-related donor; NPM1, nucleophosmin 1; PB, peripheral blood; RIC, reduced-intensity conditioning; URD, unrelated donor; wt, wild-type.

interval between the day of alloSCT and the day of death or last follow-up, and LFS as the interval between alloSCT and the date of leukemia persistence, relapse, progression, or death. NRM was defined as death from any cause without relapse or progression. GRFS was defined as survival without acute GVHD grades III–IV, chronic GVHD requiring systemic treatment, relapse, or death.¹³ RIC was defined using EBMT guidelines.¹⁴

2.3 | Statistical analysis

Descriptive statistics were presented using median, range (from minimum to maximum), and interquartile range for continuous data, frequency, and percentages for categorical data. Survivors were censored at the last contact. Cumulative incidence was used to estimate the endpoints of NRM, RI, acute, and chronic GVHD to accommodate for competing risks. Relapse and death were considered competing events for acute and chronic GVHD. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method. The median follow-up has been estimated using the reverse Kaplan–Meier method.

A Cox proportional-hazards model was performed for multivariable regressions among patients transplanted in CR1, as they represented the largest and most homogenous cohort. Results were expressed as a hazard ratio (HR) and a 95% confidence interval (95% CI). All tests were 2-sided. Type I error rate was fixed at 0.05 for factors associated with time-to-event outcomes. Analyses were performed using R 4.3.2.

3 | RESULTS

3.1 | Patient and transplant characteristics

Sixty patients with AML harboring t(8;16) who had received alloSCT were identified, among them, 44 had been transplanted in CR1. Median follow-up from alloSCT was 72.3 months. The median age at alloSCT was 46.3 years, 73% of patients were female, and 38% had secondary or treatment-related AML (AML/tAML), with lymphoid neoplasms and breast cancer being the most frequent primary malignancies. KPS was >80% in 54 patients (see Table 1 and Table S1 for further details).

The basic characteristics of the 44 patients transplanted in CR1 were comparable to the entire cohort (Table 1). Twenty-two of these patients had de novo and 22 had sAML/tAML. According to the ELN 2017 classification (not yet including t(8;16) as a factor for poor prognosis),¹⁵ 54.5% had an intermediate and 45.5% an adverse genetic risk. Furthermore, 17 (39%) patients had a CK. Donors were matched related in 34%, matched unrelated in 54%, haploidentical in 5%, and cord blood in 7%. Conditioning was myeloablative in 52%.

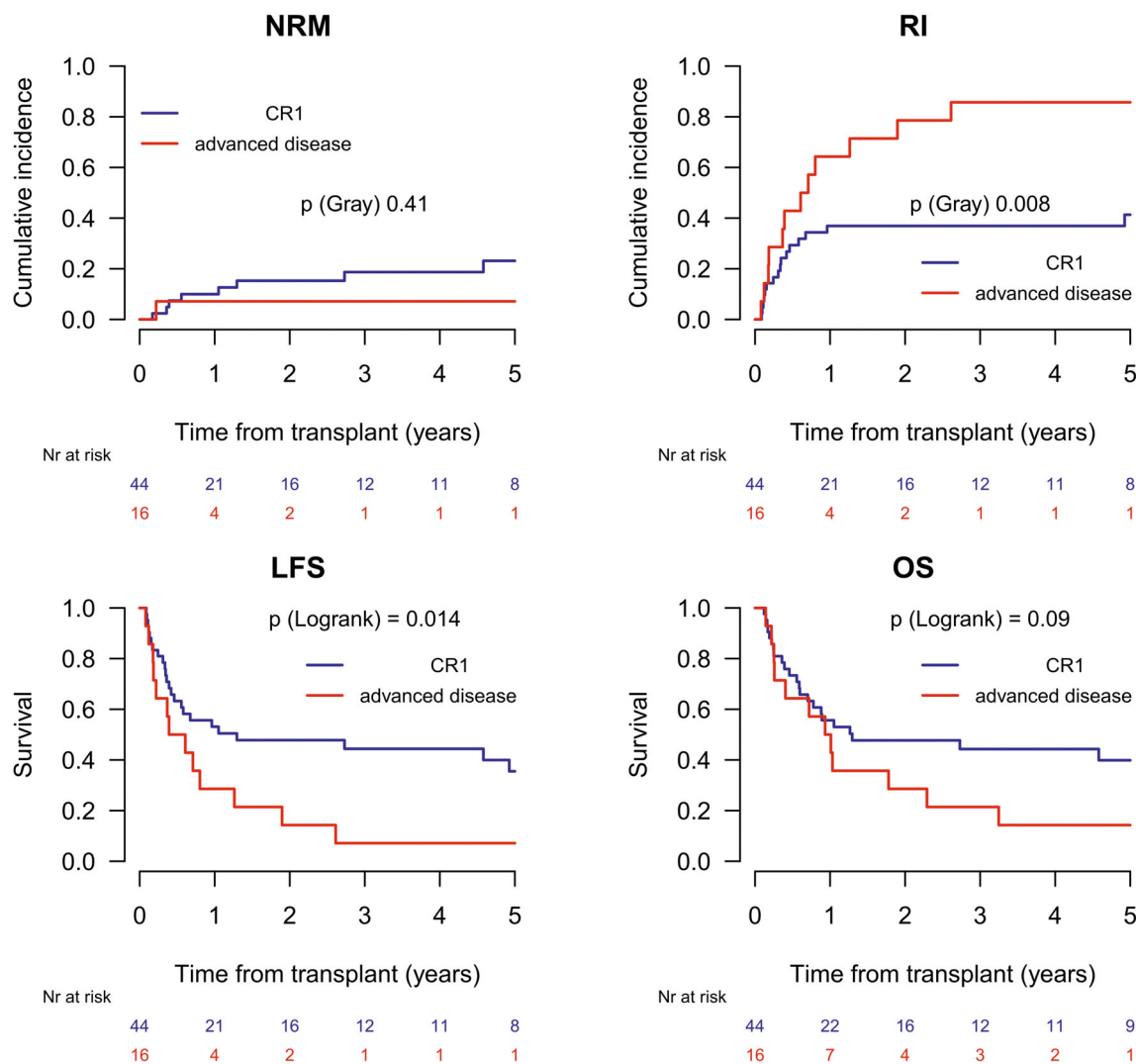
3.2 | Outcome

For the entire cohort, 2-/5-year OS and LFS from alloSCT were 42.7/32.2% and 38.9%/27.9%, respectively. Cumulative RI at 2 and 5 years was 48%/53.5%, with a median interval between alloSCT and relapse of 4.3 months (range: 1–59). Rates of NRM at 2 and 5 years were 13.1%/18.6%, respectively. The incidence of acute

TABLE 2 Comparison of outcomes at 2/5 years after allogeneic stem cell transplantation in patients transplanted in first complete remission versus advanced stages.

Outcome	CR1 [95% CI]		Advanced stages [95% CI]		p value
	2 years	5 years	2 years	5 years	
Relapse incidence	36.9% [22.2–51.7]	41.34% [24.84–57.11]	78.6% [42.1–93.5]	85.71% [44.61–97.1]	.008
Non-relapse mortality	15.3% [6.1–28.4]	23.1% [10.2–39.1]	7.1% [0.4–28.9]	7.1% [0.4–28.9]	.41
Leukemia-free survival	48% [31.8–62.2]	35.5% [19.5–51.9]	14.3% [2.3–36.6]	7.1% [0.5–27.5]	.014
Overall survival	48% [31.6–62.1]	39.9% [23.7–55.6]	28.6% [8.8–52.4]	14.3% [2.3–36.6]	.09
GVHD/relapse-free survival	37.7% [22.9–52.4]	25.7% [12–41.9]	14.3% [2.3–36.6]	7.1% [0.5–27.5]	.051

Abbreviations: CR1: first complete remission, GVHD: graft-versus-host disease.

**FIGURE 1** Outcome of AML with t(8;16) transplanted in first complete remission versus in advanced disease. Non-relapse mortality (NRM), cumulative incidence of relapse (RI), leukemia-free survival (LFS), and overall survival (OS) after allogeneic stem cell transplantation for patients with t(8;16) transplanted in first complete remission (CR1) versus in advanced disease. [Color figure can be viewed at wileyonlinelibrary.com]

GVHD°II–IV was 25%. Recurrence of the original disease was the leading cause of death (77%).

Among patients transplanted in CR1, 2-/5-year OS from alloSCT was 48%/39.9%, and the respective LFS was 48%/35.5%. The incidence

of acute GVHD was similar as in the entire cohort. The 2-/5-year RI and NRM were 36.9%/41.3% and 15.3%/23.1%, respectively (Table 2). In contrast, patients transplanted in advanced disease had a 2-/5-year RI of 78.6%/85.7%, and 2-/5-year OS and LFS were 28.6%/14.3% and

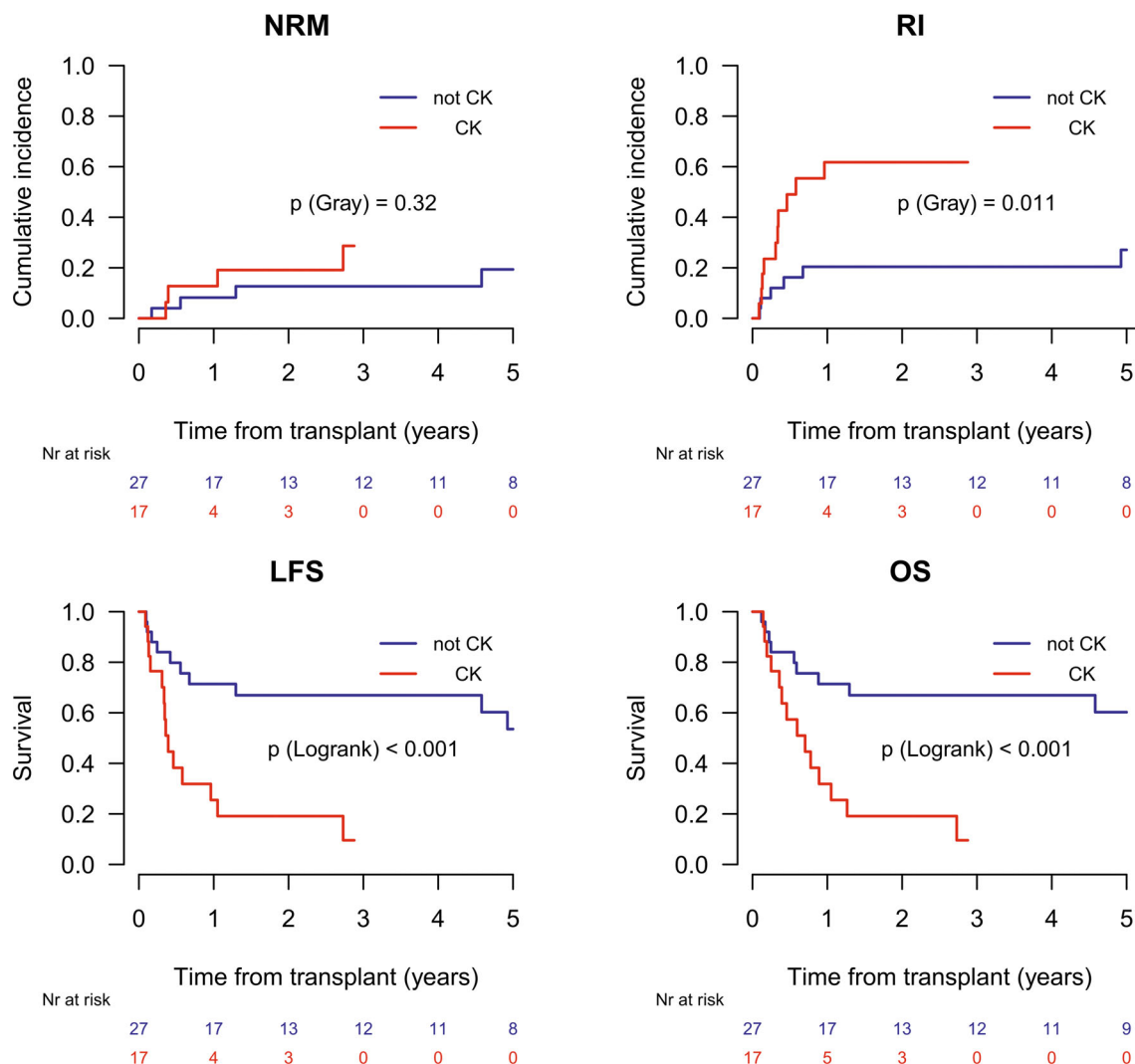


FIGURE 2 Outcome of AML with t(8;16) with and without complex karyotype transplanted in first complete remission. Non-relapse mortality (NRM), cumulative incidence of relapse (RI), leukemia-free survival (LFS), and overall survival (OS) after allogeneic stem cell transplantation for patients with t(8;16) with and without complex karyotype (CK). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ajh.27496)]

14.3%/7.1%, respectively (Table 2, Figure 1). When dissecting the genetic background of t(8;16), patients with AML with t(8;16) without a CK transplanted in CR1 showed a 2-year RI of 20.4%, OS of 66.9% and LFS of 66.9%. In contrast, 2-year OS and LFS among patients harboring t(8;16) within a CK after alloSCT in CR1 was only 19%, with a 2-year RI of 61.8% (Figure 2).

3.3 | Risk factors among patients transplanted in CR1

Descriptive results from the univariate analysis of risk factors are provided in Table S2. A multivariable analysis (MVA) revealed harboring t(8;16) within a CK as a major risk factor for outcomes, being associated with higher RI (HR 4.17, $p = .016$), lower LFS (HR 3.38, $p = .01$), lower OS (HR 3.08, $p = .017$), and lower GRFS (HR 2.9, $p = .01$). Besides, sAML was identified as an additional, independent

risk factor for RI (HR 3.73, $p = .026$). Despite the increasing use of RIC in elderly patients, age above the median of 48 years was the major risk factor for NRM ($p = .034$), reaching a 2-year NRM rate of 5% in contrast to 26.5% in younger patients ($p = .02$, Table S2). Results of the MVA are provided in Table 3 and Table S3.

4 | DISCUSSION

The aim of our study was to evaluate the role of alloSCT in the treatment of patients with AML harboring the relatively rare adverse-risk translocation t(8;16). Specifically, we were interested in the capability of alloSCT to reverse the unfavorable prognosis of the abnormality observed in previous studies, which included limited numbers of transplanted patients. The cohort identified for the present analysis triplicates the number of transplanted patients reported so far, with a reasonable follow-up of more than 6 years. Patient characteristics

TABLE 3 Multivariable analysis of risk factors for outcome at 2 years from allogeneic stem cell transplantation in first complete remission.

Variable	RI		NRM		LFS		OS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age > 48 years (median)	0.92 (0.28–2.99)	.89	10.7 (1.2–95.72)	.034	1.97 (0.73–5.3)	.18	2.12 (0.79–5.67)	.13
MRD versus other donors	0.85 (0.29–2.5)	.77	1.43 (0.28–7.42)	.67	0.98 (0.41–2.34)	.96	1.13 (0.47–2.74)	.78
CK versus no CK	4.17 (1.3–13.38)	.016	2.48 (0.5–12.27)	.27	3.38 (1.34–8.48)	.01	3.08 (1.22–7.74)	.017
Secondary AML	3.73 (1.17–11.88)	.026	0.66 (0.15–2.96)	.59	1.99 (0.83–4.78)	.12	1.92 (0.8–4.61)	.14

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CK, complex karyotype; HR, hazard ratio; LFS, leukemia-free survival; MRD, matched-related donor; NRM, non-relapse mortality; OS, overall survival; RI, relapse incidence.

corresponded well to the largest described population,⁷ with respect to age, performance score, female preponderance, and a relatively high proportion of patients with sAML/tAML and patients with complex karyotype disease.

By showing a 2-/5-year OS and LFS of 48/40% and 48/36%, overall results confirm earlier data on the outcome of alloSCT in CR1, whereas results obtained after alloSCT beyond CR1 were clearly inferior. In line with the unacceptable 5-year OS of 11% in patients who had received consolidation with conventional chemotherapy described by Kayser et al.,⁷ these findings underscore the important role of an early, consolidative alloSCT.

Patient numbers in our cohort permitted a risk factor analysis among patients transplanted in CR1. Factors related to the transplant procedure—such as choice of donor and conditioning—did not show a significant influence on outcome. Increased NRM counterbalanced the reduced relapse risk after alternative donor transplantation, whereas the Graft-versus-Leukemia-based effect of RIC seemed to be comparable to myeloablative therapy in this biological subgroup of patients transplanted in CR1. In contrast, harboring t(8;16) outside of a CK was the most important factor for improved survival. These patients reached a 5-year OS of 67%, which is comparable to outcomes of patients with an intermediate risk profile receiving alloSCT.¹⁶ Thus, alloSCT in CR1 may counterbalance the adverse risk of t(8;16) among patients not harboring a CK. It could also be hypothesized that AML with t(8;16) outside a CK in general does not represent a biological subgroup with a poor prognosis. This can neither be proven nor ruled out by our analysis, nor by data from the literature. However, as outlined by Kayser et al.,⁷ t(8;16) as such is associated with a higher susceptibility toward leukemogenesis and genomic instability. Treatment with chemotherapy alone has resulted in dismal survival outcomes. Hence, from the clinician's point of view, available data suggest that alloSCT in CR1 should be the standard of care in these patients whenever possible.

As a consequence of an increased relapse rate, patients with t(8;16) as part of a CK showed a 2-year OS and LFS of 19% only, thereby emphasizing the need for innovative concepts in this subgroup of patients. In a joint retrospective analysis by the ALWP of EBMT and the MD Anderson Cancer Center, including 1342 transplant recipients with CK AML, patients transplanted in CR1 had achieved a 2-year LFS of 38.4%.¹⁷ Hence, within the poor prognostic subgroup of CK AML, t(8;16) as part of the CK might define a

different disease biology which is a more complex clonal evolution, conferring a higher risk of relapse. In this context, it might be of interest that among the 19 patients from our cohort with a detailed description of their CK available, the aberrations typically associated with a complex karyotype (such as $-5/\text{del}5q$, $-7/\text{del}7q$, and $-17/\text{del}17p/\text{i}17q$) [16], were found in only 3 patients (data not shown).

Having sAML/tAML was another risk factor identified in the MVA, which was significantly associated with increased relapse risk. Independently from genetics, a prior registry analysis had shown an inferior prognosis of patients with sAML/tAML in general, even after alloSCT.¹⁸ Nevertheless, in contrast to the observation by Kayser et al.,⁷ who had not found any patient with sAML/tAML and t(8;16) being rescued by alloSCT, a 5-year OS of 36% after alloSCT in CR1 could be demonstrated in the present analysis. Hence, alloSCT can also be offered as consolidation to patients with sAML/tAML and t(8;16).

Due to the retrospective nature of the study, several limitations must be considered. These include missing information on molecular residual disease status and on pre- and post-transplant therapies. Furthermore, information on additional molecular aberrations apart from mutations in *FLT3*- and *NPM1*-genes were not available. A high frequency of additional mutations has been hypothesized by Kayser et al., based on their observation in 10 patients. However, no particular association with any aberration known to influence sensitivity to chemotherapy or alloSCT has been described.⁷ Finally, factors that have influenced the individual decision for allocating patients to alloSCT such as information on relevant comorbidities and availability of a suitable donor, as well as factors for the choice of conditioning could not be identified retrospectively, which is why we cannot exclude a bias in terms of patient selection and treatment.

In conclusion, according to the largest series analyzed in this setting so far, we can emphasize the important role of alloSCT as consolidation for t(8;16) AML. Especially patients without multiple additional cytogenetic abnormalities achieved a low risk of relapse and a 5-year OS >60%. Hence, in this subgroup, alloSCT in CR1 appears to compensate for the unfavorable prognostic value of this translocation and should therefore be recommended to eligible patients. Whether or not t(8;16) has any additional role in the disease biology or the clinical outcome of patients with a CK remains to be evaluated. Innovative strategies including or not alloSCT concepts are highly warranted in these patients.

AUTHOR CONTRIBUTIONS

AKS analyzed data, interpreted results, and drafted the manuscript. ML performed statistical analysis and created the figures. JV, MPGH, ME, PB, GS, PC, EF, AN, FB, AB, GB, and AN contributed to data collection and revised the manuscript. JE, MM, and FC contributed to data collection, designed the study, and revised the manuscript. CS designed the study, contributed to data collection, analyzed data, interpreted results, and drafted the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data was allocated by the EBMT registry in Paris. The datasets are available upon data-specific request.

PATIENT CONSENT

All patients have provided informed consent, authorizing the use of their personal information for research purposes.

ORCID

Ann-Kristin Schmälter  <https://orcid.org/0000-0002-4498-8685>

Patrice Chevallier  <https://orcid.org/0000-0003-3142-5581>

Ali Bazarbachi  <https://orcid.org/0000-0002-7171-4997>

Gesine Bug  <https://orcid.org/0000-0003-2359-131X>

Arnon Nagler  <https://orcid.org/0000-0002-0763-1265>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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