

Allogeneic hematopoietic cell transplantation improves outcome of adults with t(6;9) acute myeloid leukemia: results from an international collaborative study

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ABSTRACT

Acute myeloid leukemia (AML) with t(6;9)(p22;q34) is a distinct entity accounting for 1-2% of AML cases. A substantial proportion of these patients have a concomitant *FLT3*-ITD. While outcomes are dismal with intensive chemotherapy, limited evidence suggests allogeneic hematopoietic cell transplantation (allo-HCT) may improve survival if performed early during first complete remission. We report on a cohort of 178 patients with t(6;9)(p22;q34) within an international, multicenter collaboration. Median age was 46 years (range: 16-76), AML was *de novo* in 88%, *FLT3*-ITD was present in 62%, and additional cytogenetic abnormalities in 21%. Complete remission was achieved in 81% (n=144), including 14 patients who received high-dose cytarabine after initial induction failure. With a median follow up of 5.43 years, estimated overall survival at five years was 38% (95%CI: 31-47%). Allo-HCT was performed in 117 (66%) patients, including 89 in first complete remission. Allo-HCT in first com-



Ferrata Storti Foundation

Haematologica 2020
Volume 105(1):161-169

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Received: January 21, 2019.

Accepted: April 15, 2019.

Pre-published: April 19, 2019.

doi:10.3324/haematol.2018.208678

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/105/1/161

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plete remission was associated with higher 5-year relapse-free and overall survival as compared to consolidation chemotherapy: 45% (95%CI: 35-59%) and 53% (95%CI: 42-66%) versus 7% (95%CI: 3-19%) and 23% (95%CI: 13-38%), respectively. For patients undergoing allo-HCT, there was no difference in overall survival rates at five years according to whether it was performed in first [53% (95%CI: 42-66%)], or second [58% (95%CI: 31-100%); n=10] complete remission or with active disease/relapse [54% (95%CI: 34-84%); n=18] ($P=0.67$). Neither *FLT3*-ITD nor additional chromosomal abnormalities impacted survival. In conclusion, outcomes of t(6;9)(p22;q34) AML are poor with chemotherapy, and can be substantially improved with allo-HCT.

Introduction

Acute myeloid leukemia (AML) with t(6;9)(p22;q34) has been listed as a distinct entity in the World Health Organization classification since 2008 and accounts for a small group (1-2%) of AML patients.^{1,2} The translocation t(6;9), first described in AML in 1976,³ results in formation of the *DEK-NUP214* chimeric fusion gene, where *DEK* at 6p22³ is fused to *NUP214* (formerly known as *CAN*), located at 9q34.⁴ This fusion gene acts as an aberrant transcription factor and alters nuclear transport by binding soluble transport factors.⁵ In addition, *DEK-NUP214* has been reported to enhance protein synthesis in myeloid cells.^{6,7} In a murine model, *DEK-NUP214* induced leukemia when transduced to long-term repopulating stem cells.⁸

Acute myeloid leukemia with t(6;9) occurs in children and adults, as reported in a retrospective cohort analysis of 69 patients (31 children and 38 adults) with a median age of 23 years, most of whom presented with *de novo* AML.² Of note, 42-69% of pediatric and 73-90% of adult AML patients with t(6;9) are described to harbor a concomitant internal tandem duplication of the *FLT3* gene (*FLT3*-ITD),^{2,9-13} while secondary cytogenetic abnormalities are observed in 12-19% of pediatric and adult patients.^{2,13}

Clinically, t(6;9) AML has been associated with a poor prognosis in children and adults,^{2,12-15} with reported 5-year overall survival (OS) rates of 28% and 9%, respectively.² With this, adult patients with this translocation are categorized into the adverse risk group according to the National Comprehensive Cancer Network guidelines.¹⁶ Allogeneic hematopoietic cell transplantation (allo-HCT) may improve survival if performed during first complete remission (CR1).^{2,17} However, the results were hampered by the small number of patients. Even results derived from a large registry data base were inconclusive on this issue due to missing data on allo-HCT.¹⁵ Additionally, results on AML patients with t(6;9)(p22;q34) are rarely reported, although these patients were included in a recent large randomized trial.¹⁸ Thus, international multicenter cohort studies are the only opportunity to better describe characteristics and evaluate outcome according to treatment strategies.

The objectives of our study were to characterize a large cohort of AML patients with t(6;9)(p22;q34) in an international, multicenter cohort and to evaluate outcomes according to treatment.

Methods

Patients and treatment

Information on 178 patients with AML and t(6;9)(p22;q34) diagnosed between 1989 and 2016 was collected from fourteen

study groups/institutions in the US and Europe. Participating centers were chosen upon network relationships of the first and last author. Detailed case report forms (including information on baseline characteristics, chemotherapy, allo-HCT, response, and survival) were collected from all participating centers. Inclusion criteria were adult patients with t(6;9)(p22;q34), eligible for intensive therapy (ECOG 0-2), including (but not limited to) allo-HCT. All patients who fulfilled these criteria were included by the participating groups/institutions, respectively. Diagnosis of AML was based on French-American-British Cooperative Group criteria¹⁹ and, after 2003, on revised International Working Group criteria.²⁰ Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.²¹ *FLT3* mutation screening for internal tandem duplications (ITD) and point mutations within the tyrosine kinase domain (TKD) was carried out at each institution per local practice.^{10,22} Data collection and analysis were approved by the Institutional Review Boards of the participating centers.

Treatment

One-hundred and seventy-six of the 178 patients (99%) received intensive induction treatment either within clinical trials (n=116) or according to local institutional standards (n=62). Treatment protocols included the Study Alliance Leukemia (SAL) AML96²³ and AML2003²⁴ trials, the United Kingdom AML10¹⁵ AML11,²⁵ AML12,¹⁵ AML14,²⁵ AML15,¹⁵ AML16²⁶ and AML17²⁷ protocols, as well as the ALFA 9801,²⁸ 9802²⁹ and 0702³⁰ trials. Induction therapy according to local standard most frequently consisted of the 7+3 regimen of anthracycline plus cytarabine (n=53). Two patients (1%) received either azacitidine or decitabine as induction therapy and both went on to allo-HCT. Response was assessed according to International Working Group recommendations.²⁰ All studies were approved by the institutional review boards of the participating centers. All patients provided written informed consent for participation in one of the treatment trials or for therapy according to local standards.

Statistical analysis

Survival end points including OS, relapse-free survival (RFS), cumulative incidence of relapse (CIR), and cumulative incidence of death in CR (CID) were defined according to the revised recommendations of the International Working Group.²⁰ Comparisons of patients' characteristics were performed with the Kruskal-Wallis rank sum test for continuous variables and Fisher's exact test for categorical variables. The median follow-up time was computed using the reverse Kaplan-Meier estimate.³¹ The Kaplan-Meier method was used to estimate the distribution of RFS and OS.³² Confidence interval (CI) estimation for survival curves was based on the cumulative hazard function using Greenwood's formula for variance estimation. Log rank tests were employed to compare survival curves between groups. A Cox proportional hazards regression model was used to identify

prognostic variables for OS.³³ The following variables were included in the Cox models: age at diagnosis, gender, logarithm of white blood cells, platelet count, *FLT3*-ITD mutational status, and detection of additional cytogenetic abnormalities. The effect of allo-HCT on OS as a time-dependent intervening event was tested by using the Mantel-Byar method³⁴ for univariable and Andersen-Gill model for multivariable analyses.³⁵ The method of Simon and Makuch was used to estimate survival distributions with respect to time-dependent interventions.³⁶

The individuals at risk were initially all represented in the chemotherapy group. If patients received an allo-HCT, they were censored at this time point in the chemotherapy group and further followed up within the allo-HCT group.

Cumulative incidence of relapse and CID and their standard errors were computed according to the method described by Gray³⁷ and included only patients attaining CR. Missing data were replaced by 50 imputations using multivariate imputations by chained equations applying predictive mean matching.³⁸ Backward selection applying a stopping rule based on *P*-values was used in multivariable regression models to exclude redundant or unnecessary variables. All statistical analyses were performed with the R statistical software environment, version 3.3.1, using the R packages *prodlm*, version 1.5.7, and *survival*, version 2.39-5.³⁹

Results

Study cohort

Overall demographic and clinical data were collected from 178 patients (MRC, *n*=75; SAL, *n*=27; Fred Hutchinson Cancer Research Center, Seattle, *n*=12; ALFA, *n*=12; Dana-Faber Cancer Institute and Massachusetts General Hospital, Boston, *n*=12; Johns Hopkins University, Baltimore, *n*=8; Charité-University Medical Center Berlin, *n*=7; University of Maryland Greenebaum Comprehensive Cancer Center, *n*=6; Memorial Sloan Kettering Cancer Center, New York, *n*=6; Perelman School of Medicine at the University of Pennsylvania, *n*=4; Mayo Clinic Rochester, *n*=4; Czech Leukemia Centers, *n*=4; University Hospital Bonn, *n*=1) diagnosed with t(6;9)(p22;q34) AML between 1989 and 2016. Baseline characteristics are summarized in Table 1; median age was 46 years (range: 16-76) and 82 patients (46%) were female. Type of AML was *de novo* in 157 (88%), therapy-related in 4 (2%), and secondary after previous myelodysplastic syndrome (MDS)/myeloproliferative neoplasm in 12 (7%) patients. In addition, five (3%) patients with MDS treated intensively according to AML protocols were included in this analysis. Median white blood cell (WBC) count was $16.6 \times 10^9/L$ (range: 0.5-274) and was significantly higher in patients with, compared to without, *FLT3*-ITD (*P*=0.02).

Cytogenetic and molecular analyses

The balanced translocation t(6;9)(p22;q34) was the sole abnormality in 140 (79%) patients, while additional cytogenetic abnormalities were present in 38 (21%). Of note, trisomy 13 was present in ten patients, either as a sole additional abnormality (*n*=1), in combination with trisomy 8 (*n*=2) or with another balanced translocation (*n*=2), or within a complex karyotype characterized by gains only (*n*=5). *FLT3*-ITD molecular testing was available in 127 (71%) patients and 79 (62%) had *FLT3*-ITD. *FLT3*-TKD mutational status was available in 76 (43%) and 4 (5%) were mutated (Table 1).

Response to induction therapy

Data on response to induction therapy were available in all patients. Early death (ED) occurred in two (1%) patients. Overall, CR was achieved in 144 patients (81%). Thirty-five patients with initial induction failure received a salvage therapy [high-dose cytarabine (HiDAC)-based, *n*=23; other intensive, *n*=3; not intensive, *n*=4; unknown, *n*=5] and 23 of them achieved a CR (66%), including 14 after HiDAC. The CR rate in patients with *FLT3*-ITD was 81% (64 of 79 patients) as compared to 77% (37 of 48 patients) in patients without *FLT3*-ITD (*P*=0.65). No prognostic factors for CR achievement were identified within the available baseline characteristics. Two of five patients with MDS achieved a CR according to AML criteria. In six patients with *FLT3*-ITD treated on the AML15 (*n*=2) or AML17 (*n*=4) trials, lestaurtinib⁴⁰ was added to induction therapy and all patients achieved a CR.

Further therapy including intensive consolidation and allogeneic hematopoietic stem cell transplantation

Fifty-five (38%) of 144 patients in CR1 received intensive consolidation chemotherapy without transplantation, whereas 89 (62%) proceeded to allo-HCT. The majority of the patients (*n*=52 of 89, 58%) who went on to allo-HCT received a consolidation therapy prior to transplant.

Relapses occurred in 47 (85%) patients after consolidation chemotherapy and in 28 (31%) after allo-HCT in CR1. Relapsed patients without allo-HCT died after in median 5.4 months (range: 1-31.6 months). Twenty-one patients who relapsed after allo-HCT died.

Three patients died after consolidation chemotherapy and seventeen in CR after allo-HCT in CR1, mainly due to graft-versus-host disease (GvHD; *n*=5) or infections (*n*=4).

Tyrosine kinase inhibitors (TKI) were given after relapse in seven patients with *FLT3*-ITD, either as single agents (*n*=6) or in combination with chemotherapy (*n*=1) (post allo-HCT, *n*=4; post chemotherapy, *n*=3). A CR2 was achieved in one patient after treatment with gilteritinib⁴¹ and a second patient achieved CR2 with incomplete hematologic recovery (CRi) after treatment with lestaurtinib in combination with mitoxantrone/etoposide/cytarabine. The first patient died in CR one month after initiation of gilteritinib due to a perforated intestine and sepsis. The second patient relapsed six months after achieving CR2 and received donor lymphocytes, but died six months later due to progressive disease. Another patient was salvaged with quizartinib and achieved a partial remission (9% blast cells in bone marrow). The patient then went on to allo-HCT, but died one month later due to GvHD. Treatment with either gilteritinib or sorafenib was not successful in the other four patients.

Allogeneic hematopoietic stem cell transplantation in second complete remission

Among patients not proceeding to allo-HCT in CR1, ten patients were transplanted in CR2. Of those, six have died at a median of 16.5 months after allo-HCT. Causes of death in CR were infection (*n*=2), graft failure (*n*=1), multi-organ failure (*n*=1), and unknown (*n*=1). One patient relapsed and died due to AML.

Allogeneic hematopoietic stem cell transplantation with residual disease

In 34 patients not achieving a CR after intensive induction therapy, 15 (44%) proceeded to allo-HCT with active

disease. Of those, six patients are still in CR after a median follow up of 66.5 months (range: 11.8-110.8 months) and two patients achieved CR2 after relapse and are still in CR, whereas seven patients died (transplant-related mortality, n=4; refractory AML after relapse, n=2; pulmonary embolism 7.9 years after transplant, n=1).

Allogeneic hematopoietic stem cell transplantation after relapse

Three patients proceeded to allo-HCT with active disease after relapse and all of these patients died. Causes of death included infection after 56 days in one and GvHD

15 days after transplant in another patient. One patient died due to refractory AML after relapse.

Characteristics of patients undergoing allogeneic hematopoietic stem cell transplantation

Overall, an allo-HCT was performed in 117 of the 178 patients (66%), either in CR1 (n=89) or CR2 (n=10), with refractory disease (n=15) or after relapse (n=3) with no differences in baseline characteristics between groups (Table 1).

The majority of patients (n=76) received myeloablative conditioning, including total body irradiation (TBI) in 39

Table 1. Baseline characteristics of patients with acute myeloid leukemia and t(6;9)(p22;q34).

	All patients (n=178)	Subset of patients undergoing allo-HCT in CR (n=99)	Subset of patients undergoing allo-HCT with active disease/ relapse (n=18)
Median age (years) (Range)	46 (16-76)	43 (16-71)	46 (19-69)
Male gender, n (%)	96 (54)	57 (58)	9 (50)
Median WBC, x10 ⁹ /L (Range)	16.6 (0.5-274)	13.1 (0.5-274)	16.3 (1.5-200.4)
Missing	12	8	1
Median hemoglobin, g/dL (Range)	8.6 (3.2-14.2)	8.6 (3.2-14.2)	9 (4.6-13.1)
Missing	29	18	2
Median platelets, x10 ⁹ /L (Range)	53 (7-451)	53 (7-451)	59 (10-229)
Missing	21	13	2
Median BM blasts, % (Range)	60 (7-100)	55 (10-100)	60 (7-90)
Missing	22	12	1
Cytogenetics, n (%)			
As sole aberration	140 (79)	79 (80)	14 (78)
Including +13*	10 (6)	6 (6)	–
Sole +13	1	–	–
+ 8, +13	2	1	–
Other complex**	11 (6)	6 (6)	1 (6)
Nullisomy XY	4 (2)	–	2 (11)
Other [†]	13 (7)	7 (7)	1 (6)
Disease type, n (%)			
<i>De novo</i> AML	157 (88)	88 (89)	15 (83)
s-AML	12 (7)	7 (7)	1 (6)
t-AML	4 (2)	3 (3)	–
MDS	5 (3)	1 (1)	2 (11)
FLT3-ITD			
n (%)	79 (62)	43 (57)	9 (60)
Missing	51	25	3
FLT3-TKD			
n (%)	4 (5)	4 (8)	–
Missing	102	48	9

allo; allogeneic; AML: acute myeloid leukemia; BM: bone marrow; CR: complete remission; FLT3: fms-related tyrosine kinase 3; HCT: hematopoietic cell transplantation; ITD: internal tandem duplication; s-AML: AML after previous myelodysplastic syndrome / myeloproliferative neoplasm; t-AML: therapy-related AML; TKD: tyrosine kinase domain; WBC: white blood cell count. *Within a complex karyotype characterized by gains only (n=5). **Within a complex karyotype characterized by losses and unbalanced translocations. †Other than +8/+13/nullisomy XY. Results may not add-up to 100 due to rounding.

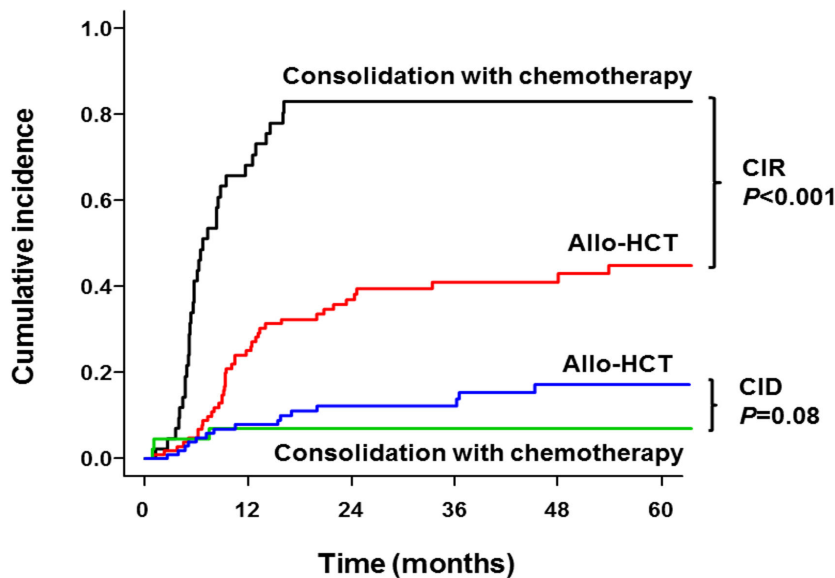


Figure 1. Cumulative incidence of relapse (CIR) and cumulative incidence of death (CID) according to treatment strategy. CIR and CID included only patients achieving complete remission.

Table 2. Relapse-free and overall survival according to treatment strategy in first complete remission.

	5-years RFS %	95%-CI	5-year OS %	95%-CI
Allo-HCT (n=89)	45	35-59	53	42-66
Consolidation chemotherapy (n=55)	7	3-19	23	13-38

allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; OS: overall survival; RFS: relapse-free survival. Median follow up was 5.43 years (95%CI: 3.93-6.53 years).

patients. Forty-one patients received reduced-intensity conditioning. Source of donor was matched related in 46, matched unrelated in 54, haplo-identical in 11, cord blood in five, and unknown in one of the 117 patients.

Cumulative incidence of relapse, cumulative incidence of death in complete remission and survival

The median follow up of the entire cohort was 5.43 years (95%CI: 3.93-6.53 years). Median and 5-year OS of the entire cohort were 2.25 years (95%CI: 1.56-3.70 years) and 38% (95%CI: 31-47%). Five-year RFS and OS were 45% (95%CI: 35-59%) and 53% (95%CI: 42-66%) in patients proceeding to allo-HCT in CR1 after induction therapy (n=89), as compared to 7% (95%CI: 3-19%;) and 23% (95%CI: 13-38%), respectively, in those who received consolidation chemotherapy alone (n=55) (Table 2). In subgroup analysis, presence of *FLT3*-ITD had no prognostic impact on OS, either in the total analyzed cohort ($P=0.093$), or in those patients proceeding to allo-HCT ($P=0.39$). Similarly, additional chromosomal abnormalities had no prognostic impact on OS in the mentioned cohorts ($P=0.49$; $P=0.86$; respectively). A Cox regression analysis revealed, after limited backward selection, higher WBC [hazard ratio (HR) for log₁₀, 1.62; 95%CI: 1.12-2.29; $P=0.005$] and age (HR for a difference of 10 years, 1.29; 95%CI: 1.12-1.50; $P=0.001$) as unfavorable variables, whereas platelet count, type of AML (*de novo* vs. therapy-related/secondary after previous MDS/myeloproliferative neoplasm), presence of *FLT3*-ITD, and additional cytogenetic aberrations had no impact on prognosis.

In 144 patients achieving CR1, CIR was significantly lower in patients proceeding to allo-HCT (n=89) as compared to those who were treated with consolidation chemotherapy (n=55; $P<0.001$). As expected, CID tended to be higher in patients proceeding to allo-HCT as compared to those receiving consolidation chemotherapy ($P=0.08$) (Figure 1).

One hundred and seventeen patients proceeded to allo-HCT in CR1 (n=89) or CR2 (n=10), or with refractory (n=15) or relapsed (n=3) disease. The influence of allo-HCT assessed as a time-dependent co-variable as post remission therapy on OS is illustrated by a Simon Makuch plot (Figure 2). In addition, Figure 3 shows a Kaplan Meier plot illustrating the influence of allo-HCT performed in CR1 on RFS. The Mantel-Byar tests revealed a significantly better OS ($P=0.001$) and RFS ($P<0.0001$) for patients proceeding to allo-HCT in CR1 as compared to consolidation with chemotherapy only. Neither type of conditioning ($P=0.90$) nor donor type (matched related donor versus matched unrelated/haplo-identical/cord blood donor; $P=0.30$) had an impact on outcome. There was no difference in OS measured from date of transplant in patients transplanted in CR1 or CR2 as compared to those with active disease ($P=0.66$) (Figure 4). An Andersen-Gill model including allo-HCT as a time-dependent variable revealed higher WBC and older age as unfavorable variables, whereas allo-HCT performed either in CR or with active disease was associated with a favorable prognosis. Decade of treatment, additional chromosomal abnormalities or *FLT3*-ITD had no prognostic impact (Table 3).

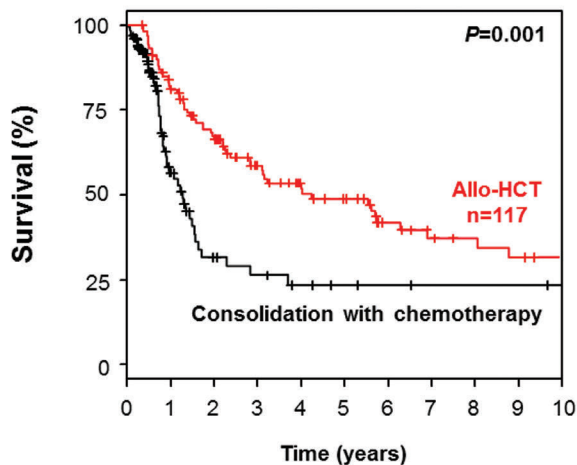


Figure 2. Simon Makuch plot evaluating the impact of allogeneic hematopoietic cell transplantation (allo-HCT) assessed as a time-dependent co-variable in comparison with chemotherapy consolidation on overall survival.

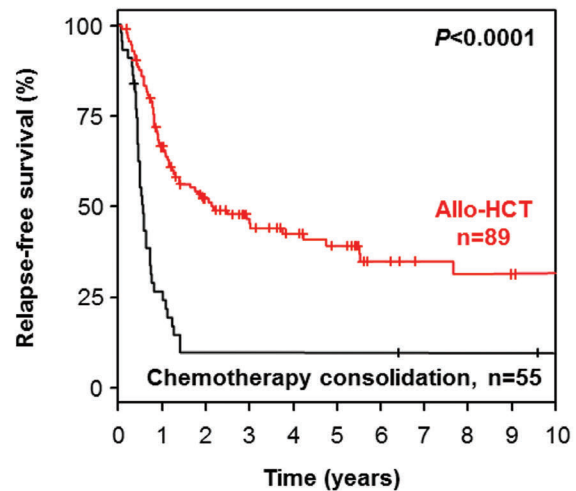


Figure 3. Kaplan Meier plot illustrating the influence of allogeneic hematopoietic cell transplantation (allo-HCT) performed in first complete remission on relapse-free survival.

Discussion

The focus of our study was to characterize adult AML patients with t(6;9) in an international cohort study and compare outcomes according to treatment strategies, with a specific focus on the impact of *FLT3* mutations as well as the impact of allo-HCT as compared to conventional chemotherapy on survival.

We studied 178 patients (AML, n=173; MDS, n=5), all harboring the balanced translocation t(6;9)(p22;q34). A concomitant *FLT3*-ITD has been described in 42-69% of pediatric and 62-90% of adult AML patients with t(6;9),^{2,9-13,42} but these reports were hampered by the availability of mutational status in only a subset of patients^{2,9,42} and/or analysis of a low patient number.⁹⁻¹² In our large cohort, with available mutational status in 71% of patients, a concomitant *FLT3*-ITD was detected in 62% and was significantly associated with higher WBC at diagnosis, which adds to previously published data.^{2,9-13,42} Preliminary data suggest that *FLT3*-ITD promotes leukemia induction by *DEK-NUP214* in a murine model.⁴³ However, a synergistic effect to explain the high coincidence of the two mutations has yet to be demonstrated. In contrast, *FLT3*-TKD mutations were uncommon in our cohort and were slightly less frequent than those reported in AML with normal cytogenetics.⁴⁴ In addition, secondary cytogenetic abnormalities were present in 21% of our patients, most commonly including trisomy 13, and/or trisomy 8, or a complex karyotype. To date, there are still conflicting data regarding the impact of *FLT3*-ITD on outcome in AML patients with t(6;9).^{13,14,45} While results of a meta-analysis in 50 adult patients indicated an association between *FLT3*-ITD mutations and an inferior outcome in t(6;9) AML,⁴⁵ others were inconclusive due to the low number of patients without *FLT3*-ITD,² or did not find a significant adverse impact in pediatric AML patients,^{13,14} which may be due to an already very dismal prognosis.¹⁴ In our large cohort, neither a concurrent *FLT3*-ITD nor the presence of additional cytogenetic abnormalities had an impact on the achievement of CR or OS, which adds to the recent eval-

Table 3. Multivariable Andersen-Gill model on overall survival.

	HR (95%-CI)	P
<i>FLT3</i> -ITD*	1.35 (0.80-2.27)	0.26
Log10(WBC)*	1.69 (1.14-2.51)	0.009
Platelets (10x10 ⁹ /L difference)	1.00 (0.95-1.04)	0.92
Female gender	1.43 (0.96-2.13)	0.08
Age (10 years difference)	1.22 (1.05-1.42)	0.01
Type of AML#	0.83 (0.44-1.56)	0.55
Additional abnormalities	1.09 (0.67-1.77)	0.74
Decade**	0.81 (0.58-1.13)	0.22
Transplant status	0.55 (0.33-0.90)	0.02

AML: acute myeloid leukemia; CI: confidence interval; HR: hazard ratio; ITD: internal tandem duplication; OS: overall survival; WBC: white blood cell count. *Sensitivity analysis revealed no significant interaction between transplant status and *FLT3*-ITD ($P=0.44$) or WBC ($P=0.12$) **Decade, 1989-1999, 2000-2009, 2010-2016. #Type of AML denotes: *de novo* versus therapy-related/secondary after previous myelodysplastic syndrome/myeloproliferative neoplasm.

uation by the European Society for Blood and Marrow Transplantation (EBMT).⁴²

Previous publications in adult AML patients with t(6;9) reported a fairly low CR rate of 33-58% in adult patients.^{2,46} In contrast to these reports, we observed a high CR rate of 81%. The favorable CR rate in our cohort after intensive chemotherapy was in part due to a high response rate of 66% after intensive salvage chemotherapy in patients with failure after standard induction therapy. Intensive combination chemotherapy that incorporates higher doses of cytarabine is frequently used in patients with relapsed/refractory AML, but no specific salvage regimen has emerged as standard. While CR/CRi rates with intensive combination chemotherapy were overall below 40% and nearly similar in refractory (36%) and relapsed AML (36.8%),^{47,48} the observed CR rate of 66% in our cohort points to a high sensitivity towards higher doses of cytarabine in patients with initial induction failure. Particularly patients with adverse-risk cytogenetics or *FLT3*-ITD were shown to benefit from HiDAC

therapy.⁴⁹ Therefore, the HiDAC approach might be beneficial in patients with t(6;9) and should be addressed further.

In addition, anthracycline dose intensification during induction therapy with daunorubicin at 90 mg/m² has been shown to have a beneficial impact,²⁷ not only in patients with core-binding factor leukemia,⁵⁰ but also in patients with *FLT3*-ITD.^{27,51} Although our analysis included patients from the AML17 trial (n=22), which studied high-dose daunorubicin, no meaningful analysis could be made due to the low number of patients.

In our analysis, we found that allo-HCT resulted in an excellent RFS and OS, which is in line with the data of Ishiyama *et al.*¹⁷ In a matched-pair analysis of *de novo* AML using data from the Japanese allo-HCT data registry, they compared outcome of 57 patients with t(6;9) to that of 171 patients with normal karyotype.¹⁷ All patients received an allo-HCT between 1996 and 2007, either in CR1 or CR2 (n=116), or with active disease (n=112). In patients with t(6;9), the 5-year OS (45% vs. 40%), disease-free survival (42% vs. 33%), CIR (42 vs. 45%), and non-relapse mortality (16 vs. 22%) did not differ from those observed in AML with normal karyotype.¹⁷ Nevertheless, the results were hampered by a lack of molecular profile in the group of AML with normal karyotype, as well as lack of data on *FLT3*-ITD mutational status in AML with t(6;9). Our data are particularly impressive when compared to the dismal survival of patients with t(6;9) disease treated with chemotherapy alone. Thus, allo-HCT seems to ameliorate outcome in patients with t(6;9), with outcomes comparable to those of patients with intermediate-risk cytogenetics.⁵² As expected, CIR was significantly reduced in our cohort after allo-HCT performed in CR1 as compared to intensive consolidation chemotherapy.

Since supportive care might have impacted outcome, we have included the decade of treatment in multivariable analysis. However, this had no impact on overall survival. In addition, neither type of conditioning nor donor type had any impact on outcome. Outcome after allo-HCT was also favorable if performed in CR2, or even with active disease. Overall, this suggests the existence of a specific and very strong graft-*versus*-leukemia effect in this molecular context. Of note, recently presented data by Beya *et al.* on behalf of the EBMT demonstrated similar efficacy of allo-HCT in AML with t(6;9) transplanted in CR2 or active (relapsed/refractory) disease.⁴² Although this partly supports the finding from our cohort, we would like to emphasize that retrospectively collected data have serious limitations since the factors for allocating patients to allo-HCT, such as co-morbidities, individual assessment of the treating physician, choice of conditioning, and availability of a donor, remain unknown, and this needs to be taken into account when evaluating the value of allo-HCT in our series.

Despite the large number of patients with *FLT3*-ITD, only thirteen patients were treated with TKI, either front-line with lestaurtinib (n=6) in combination with intensive induction chemotherapy,⁴⁰ or after relapse either with single-agent gilteritinib⁴¹ or sorafenib (n=6), or with lestaurtinib in combination with intensive chemotherapy (n=1). Interestingly, all six patients who received front-line lestaurtinib + chemotherapy achieved a CR, whereas TKI treatment ± chemotherapy in relapsed patients showed limited efficacy, with only two patients achieving CR2. Currently, midostaurin is the only approved TKI in *de novo*

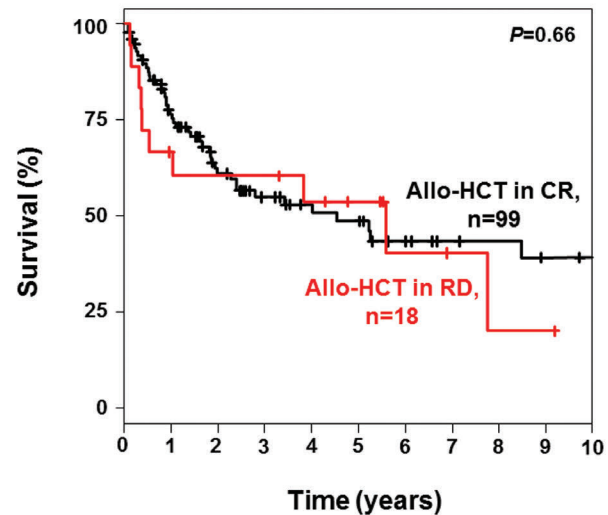


Figure 4. Overall survival after allogeneic hematopoietic cell transplantation according to remission status.

AML with *FLT3* mutations, based on the positive results from the large, international randomized phase III trial.¹⁸ The combination of midostaurin with intensive chemotherapy significantly improved OS in younger adults with *FLT3*-mutated AML, as compared to the placebo arm. In that study, patients receiving an allo-HCT in CR1 had a better outcome if they were treated with midostaurin during induction therapy, suggesting that the optimal treatment strategy in *FLT3*-mutated AML would be to move on to allo-HCT early in CR1.¹⁸ Unfortunately, no data were presented either in the manuscript or in the supplement for the small subgroup of patients characterized by t(6;9).¹⁸ Thus, the impact of adding TKI to induction chemotherapy in t(6;9) AML is currently unknown.

Conclusions

Our cohort of AML patients with t(6;9)(p22;q34) showed a high CR rate after intensive induction therapy, suggesting that these patients should be candidates for intensive induction therapy whenever possible. Despite the initial high chemo-sensitivity of the disease, treatment with consolidation chemotherapy alone resulted in dismal survival outcomes. Thus, based on our encouraging results with allo-HCT, this should be standard of care whenever possible for these patients.

Funding

SK gratefully acknowledges to be supported by the Olympia-Morata fellowship program from the Medical Faculty of the Heidelberg University as well as financial support by Deutsche Forschungsgemeinschaft within the funding program Open Access Publishing, by the Baden-Württemberg Ministry of Science, Research and the Arts and by Ruprecht-Karls-Universität Heidelberg. MJL is supported by a grant from the NCI (NCI Leukemia SPORE P50 CA100632). RBW is a Leukemia & Lymphoma Society Scholar in Clinical Research. ZR, JM, PZ and TS were supported by the Ministry of the Czech Republic, grant No. 15-25809A. Data from the AML10, AML11, AML12, AML14, AML15, AML16, and AML17 trials were supplied by Cardiff University HCTU on behalf of the NCRI AMLWG.

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