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-
The translation t(6;9), first described in AML in 1976, results in formation of the DEK-NUP214 chimeric fusion gene, where DEK at 6p22 is fused to NUP214 (formerly known as CAN), located at 9q34. This fusion gene acts as an aberrant transcript factor and alters nuclear transport by binding soluble transport factors. In addition, DEK-NUP214 has been reported to enhance protein synthesis in myeloid cells. In a murine model, DEK-NUP214 induced leukemia when transduced to long-term repopulating stem cells.

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 25 years, most of whom presented with de novo AML. Of note, 42-69% of pediatric and 75-90% of adult AML patients with t(6;9) are described to harbor a concomitant secondary cytogenetic abnormalities are observed in 12-19% of pediatric and adult patients.

Clinically, (t;6;9) AML has been associated with a poor prognosis in children and adults, with reported 5-year overall survival (OS) rates of 28% and 9%, respectively. With this, adult patients with this translocation are categorized into the adverse risk group according to the National Comprehensive Cancer Network guidelines. Allogeneic hematopoietic cell transplantation (allo-HCT) may improve survival if performed during first complete remission (CR1). 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. 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. 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 criteria and, after 2005, on revised International Working Group criteria. Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature. 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. 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) AML96, AML2003 trials, the United Kingdom AML10,25 AML12,15 AML14,25 AML15,15 AML16,26 and AML17 protocols, as well as the ALFA 9801,28 9802,30 and 0702,30 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. 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 (CIF) were defined according to the revised recommendations of the International Working Group. 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. The Kaplan-Meier method was used to estimate the distribution of RFS and OS. 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...
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 method for univariable and Andersen-Gill model for multivariable analyses. The method of Simon and Makuch was used to estimate survival distributions with respect to time-dependent interventions.

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 Gray and included only patients attaining CR. Missing data were replaced by 50 imputations using multivariate imputations by chained equations applying predictive mean matching. The method of Simon and Makuch was used to estimate survival distributions with respect to time-dependent interventions.

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 (48%) 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, lestaurtinib 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 (35%) 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 chemotheraphy, n=3). A CR2 was achieved in one patient after treatment with gilteritinib 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 withquizartinib 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

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

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

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 of 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 X/Y Results may not add up to 100 due to rounding.
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).

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

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>5-years RFS %</th>
<th>95%-CI</th>
<th>5-year OS %</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo-HCT (n=89)</td>
<td>45</td>
<td>35-59</td>
<td>53</td>
<td>42-66</td>
</tr>
<tr>
<td>Consolidation chemotherapy (n=55)</td>
<td>7</td>
<td>3-19</td>
<td>23</td>
<td>13-38</td>
</tr>
</tbody>
</table>

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).
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), but these reports were hampered by the availability of mutational status in only a subset of patients and/or analysis of a low patient number. 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. Preliminary data suggest that FLT3-ITD promotes leukemia induction by DEK-NUP214 in a murine model. 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. 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). 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, others were inconclusive due to the low number of patients without FLT3-ITD, or did not find a significant adverse impact in pediatric AML patients, which may be due to an already very dismal prognosis. 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 evaluation by the European Society for Blood and Marrow Transplantation (ERMT).

Previous publications in adult AML patients with t(6;9) reported a fairly low CR rate of 33-58% in adult patients. 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%), 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.
Currently, midostaurin is the only approved TKI in limited efficacy, with only two patients achieving CR2. 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,²⁹ but also in patients with FLT3-ITD.²⁵,²⁷ Although our analysis included patients from the AML17 trial (n=22), with 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.⁷ 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 3-year OS (45% vs. 40%), disease-free survival (42% vs. 33%), CIR (42 vs. 45%), and non-relapse mortality (16 vs. 32%) 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.⁵² 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 frontline with lestaurtinib (n=6) in combination with intensive induction chemotherapy,⁴⁹ 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 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;q54) 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.

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