Regular Article

CLINICAL TRIALS AND OBSERVATIONS

The value of allogeneic and autologous hematopoietic stem cell transplantation in prognostically favorable acute myeloid leukemia with double mutant CEBPA

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Key Points

• In AML with biallelic CEBPA-mut relapse-free survival was improved by allogeneic and autologous hematopoietic stem cell transplantation.
• In relapsed patients second complete remission rate was high and survival was favorable after an allogeneic transplantation.

The clinical value of allogeneic hematopoietic stem cell transplantation (alloHSCT) and autologous hematopoietic stem cell transplantation (autoHSCT) in the subtype of acute myeloid leukemia (AML) with double mutant CEBPA (CEBPA(dm)) has remained unsettled. Among 2983 patients analyzed for CEBPA mutational status (age 18-60 years) treated on 4 published Dutch-Belgian-Swiss Hemato-Oncology Cooperative Group (HOVON/SAKK) and 3 German-Austrian AML Study Group (AMLSG) protocols (2 published, 1 registered, clinicaltrials.gov NCT00151255), 124 had AML with CEBPA(dm) and achieved first complete remission (CR1). Evaluation of the clinical impact of alloHSCT and autoHSCT vs chemotherapy was performed by addressing time dependency in the statistical analyses. Thirty-two patients proceeded to alloHSCT from a matched related (MRD, n = 29) or a matched unrelated donor (MUD, n = 3). Survival of relapsed patients measured from date of relapse was 46% after 3 years. Adult AML patients with CEBPA(dm) benefit from alloHSCT and autoHSCT; relapsed patients still have a favorable outcome after reinduction followed by alloHSCT. (Blood. 2013;122(9):1576-1582)

Introduction

Acute myeloid leukemia (AML) with mutated CCAAT/enhancer binding protein α (CEBPA) gene represents a provisional disease entity in the current World Health Organization (WHO) classification in the category “AML with recurrent genetic abnormalities.” However, multiple studies demonstrated that AML with double mutant CEBPA (CEBPA(dm)) could be clearly distinguished from AML with single mutant CEBPA with respect to biological and prognostic features. In the majority of AML with CEBPA(dm), one allele is affected by an N-terminal mutation and the second allele carries the mutation in the C-terminus (bZIP), whereas in AML with a single mutant CEBPA, mutations occur either in the N-terminus or in the C-terminus of the gene. The previously shown favorable impact of mutant CEBPA in various independent comprehensive studies on prognosis has more recently been specifically related to the subtype of AML with CEBPA(dm).

The incidence of AML with mutated (single and double) CEBPA ranges from 7.5% to 11% of all AML patients and from about 13% to 18% in AML exhibiting a normal karyotype. Furthermore, the incidence of AML with mutated CEBPA in patients who are >60 years range from 8.5% to 18%.

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Young and middle aged adults (age 18-60 years) with AML and mutated CEBPA and especially those with CEBPA dm have a comparatively high probability of achieving a complete remission after standard “7 + 3” induction therapy with remission rates exceeding 90%. Treatment outcome data revealed a favorable prognosis with an overall survival (OS) after 5 years ranging between 50% and 70%, including different types of consolidation therapy with intensive chemotherapy, autologous hematopoietic stem cell transplantation (autoHSCT), and allogeneic hematopoietic stem cell transplantation (alloHSCT). However, relapse still remains the major cause of treatment failure that mainly occurs within the first 2 years after achieving a complete remission (CR). This has for instance raised the question whether autoHSCT and alloHSCT in CR1 should be recommended in patients with this genetic abnormality. So far, analyses according to the type of postremission treatment in CEBPA dm AML patients have not become available mainly due to limited patient numbers precluding informative statistical analyses. Thus, it still remains unclear whether the favorable prognosis of AML with CEBPA dm can be attributed to the mutation itself irrespective of the type of applied postremission therapy (ie, prognostic marker) or whether the favorable prognosis is the result of a high rate of cure after autoHSCT and alloHSCT in CR1 and after relapse (ie, predictive marker). Informative insight into these factors could be of direct clinical relevance, as it may guide treatment decisions on the application of autoHSCT and alloHSCT already in CR1 or alternatively to hold back on these approaches and reserve the option especially of an alloHSCT as salvage only in relapsed patients. To address this question, the Dutch-Belgian-Swiss Hemato-Oncology Cooperative Group (HOVON/SAKK) and the German-Austrian AML Study Group (AMLSG), as leukemia cooperative groups, performed a joint effort on an individual-patient based meta-analysis focusing on the AML CEBPA dm subtype in CR1. The aim was to evaluate different postremission strategies with a major focus on the comparison between alloHSCT, autoHSCT, and intensive chemotherapy in a large series of CEBPA dm AML patients in CR1. Furthermore, with an integrated approach, we also included treatment after relapse and its impact on outcome.

### Patients and methods

#### Patients and treatment

All patients included in this study were recruited within 2 major leukemia cohorts. AML patients from cohort I (n = 3450) were enrolled in the HOVON/SAKK trials HOVON04(A), HOVON29/SAKK30/95,15-17 HOVON42(A)/SAKK30/00, and HOVON92/SAKK30/0816-18 (information on the trials is available at www.hovon.nl). Patients received 2 successive cycles of anthracycline-cytarabine- and amsacrine-cytarabine-based remission induction chemotherapy and, subsequently, in CR1 consolidation chemotherapy, autoHSCT after myeloablative therapy according to a randomization against chemotherapy and depending on an adequate stem cell collection,19 or alloHSCT after mainly myeloablative conditioning depending on the availability of a matched related donor (MRD).

Cohort II (n = 2274) comprised patients who were enrolled in the AMLSG trials AML HD93,19 AML HD98A,20 and AMLSG 07-04 (ClinicalTrials.gov Identifier: NCT00151242). Consistently throughout all AMLSG trials, patients with AML exhibiting an intermediate-risk karyotype with mutant CEBPA were intended to receive a double induction therapy with idarubicin, cytarabine, and etoposide, and repetitive cycles of high-dose cytarabine-based consolidation therapy. or, if an HLA-matched family donor was available, an allogeneic hematopoietic stem cell transplantation (HSCT) after a myeloablative conditioning regimen.

#### Statistical analysis

The definition of CR and survival end points such as OS, cumulative incidence of relapse (CIR), and death in CR (CID), as well as relapse-free survival (RFS) were based on the recommended consensus criteria. Actuarial estimates were used for the assessment of median follow-up for survival. Patient characteristics were compared by the Kruskal-Wallis test (continuous variables) and the Fisher’s exact test (categorical variables). CIR and CID were analyzed according to the method of Gray.24 To address the time dependence of the variables alloHSCT and autoHSCT, the graphical representation, according to the method of Simon and Makuch25 was used, as well as the Mantel-Byar test, as appropriated statistical approach in univariable analyses.26 For multivariable analyses, an extended Cox regression model was used according to the method of Andersen and Gill.27 For all analyses, P < .05 was considered statistically significant. All statistical analyses were performed using the statistical software Stata Statistical Software (release 12).

#### Results

**Demographics and clinical baseline characteristics of the study population**

In this cooperative individual patient data meta-analysis, 124 CEBPA dm AML patients were included with normal karyotype or intermediate-risk cytogenetics (ages between 18 and 60 years and
Table 1. Clinical and genetic characteristics of the total cohort and according to applied postremission therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total cohort</th>
<th>AlloHSCT</th>
<th>AutoHSCT</th>
<th>no HSCT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>n = 124</td>
<td>n = 32</td>
<td>n = 20</td>
<td>n = 72</td>
<td></td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66 (53%)</td>
<td>21 (66%)</td>
<td>12 (60%)</td>
<td>33 (46%)</td>
<td>.15</td>
</tr>
<tr>
<td>Female</td>
<td>58 (47%)</td>
<td>11 (34%)</td>
<td>8 (40%)</td>
<td>39 (54%)</td>
<td></td>
</tr>
<tr>
<td>WBC, x 10^9/l</td>
<td>Median (range)</td>
<td>44 (16-60)</td>
<td>40</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Platelets, x10^11/l</td>
<td>Missing 1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow blasts, (%)</td>
<td>Median (range)</td>
<td>41 (4-319)</td>
<td>39 (11.282)</td>
<td>47 (10-115)</td>
<td>40 (4-319)</td>
</tr>
</tbody>
</table>

Cytogenetics, no. (%)

- Normal karyotype: 92 (74%) 21 (66%) 14 (70%) 57 (79%) .32
- Molecular characteristics:
  - FLT3-internal tandem duplications: 11 (9%) 5 (16%) 1 (5%) 5 (7%) .38
  - NPM1: 2 (2%) 1 (3%) 1 (5%) 1 (1%) .67

Subheadings under “de novo AML” refer to French American British classification subtypes.

CR1 after induction therapy. The patients were selected from the total study population treated in the HOVON/SAKK and AMLSG prospective multicenter clinical trials recruited between 1987 and 2009 (Figure 1). Baseline characteristics and demographics for the total cohort are shown in Table 1.

No significant difference in OS was seen between the HOVON/SAKK and the AMLSG CEBPAdm patient cohorts (n = 30 vs n = 74, Cox test; P = .36); molecular and clinical variables were comparable between the HOVON/SAKK and the AMLSG CEBPAdm patient cohorts with the exception of platelet counts (P < .02, lower in AMLSG) and bone marrow blasts (P < .0001, lower in HOVON/SAKK).

Postremission therapy, CIR, and CID in CEBPAdm patients

Distribution of postremission treatment modalities in the 124 patients was as follows: alloHSCT, n = 32 (MRD n = 29, matched unrelated donor [MUD] n = 3); autoHSCT, n = 20; intensive chemotherapy, n = 72. The median time interval from diagnosis to achievement of CR1 was 1.1 months (range 0.36-4.1) with a trend (P = .053) for a longer interval in patients who received an autoHSCT as postremission treatment (median 1.25 months) compared with those who received an alloHSCT (median 1.1 months) or chemotherapy (median 1.1 months). The median time interval from CR1 to alloHSCT and autoHSCT was 4.0 months (range 0.8-6.5) and 2.3 months (range 0.4-6.2), respectively.

In total, 45 relapses (1 after alloHSCT, 5 after autoHSCT, and 39 after intensive chemotherapy) and 19 treatment-related deaths (7 after alloHSCT, 3 after autoHSCT, and 9 after intensive chemotherapy) after a median time measured from CR1 of 10.8 months (range 4.4-61) and 15 months (range 1.2-144) occurred. This leads to estimates of CIR and CID after 5 years of 3% (SE 3%) and 24% (SE 8%) for alloHSCT, 27% (SE 11%) and 13% (SE 9%) for autoHSCT, and 58% (SE 6%) and 10% (SE 4%) for intensive chemotherapy, respectively.

Treatment after relapse

and autoHSCT (HR 0.37; \( P = .012 \)) applied in CR1 independently had a favorable prognostic impact regarding RFS (Table 3). However, apparently due to a high second CR rate after salvage therapy, the superior RFS after alloHSCT and autoHSCT did not translate into a better OS in univariable analysis (\( P = .12 \)) (Figure 3B) and multivariable analyses (Table 4).

In 45 relapsed patients, OS measured from the date of relapse was 46% (95% CI, 30-60) after 3 years (Figure 4). All patients surviving more than 2 years after having first relapsed had undergone an alloHSCT (\( n = 15 \), Figure 4).

**Discussion**

This report focuses on the evaluation of the clinical impact in CEBPA\( ^{\text{dm}} \) patients of alloHSCT and autoHSCT in comparison with intensive consolidation therapy in CR1, as well as focusing on the impact of reinduction chemotherapy and alloHSCT after relapse. To this attempt, we report on 124 adults with AML and a normal karyotype or intermediate-risk karyotypes that harbor a CEBPA\( ^{\text{dm}} \), and are aged \( \leq 60 \) years. Only 1 relapsed patient received an autoHSCT in second CR and, therefore, we were not able to evaluate the clinical impact of autoHSCT after relapse. Our results clearly show that adult AML patients with the CEBPA\( ^{\text{dm}} \) genotype significantly benefit from alloHSCT and autoHSCT in CR1 with respect to RFS.

The median follow-up time of patients still alive at the date of last contact was 62 months. RFS and OS of the whole CEBPA\( ^{\text{dm}} \) patient cohort after 5 years were 48% (95% CI, 38-57) and 63% (95% CI, 53-72), respectively. There was no difference in RFS (\( P = .24 \)) and OS (\( P = .87 \)) between patients exhibiting a normal karyotype and those with intermediate-risk karyotypes (Table 2 and Figure 2). Based on the Mantel-Byar test, including alloHSCT and autoHSCT applied in CR1 as time dependent variables, RFS is significantly superior in patients receiving an HSCT (\( P < .001 \)), with significant differences in favor of alloHSCT and autoHSCT as compared with intensive chemotherapy (\( P < .001 \) and \( P = .019 \), respectively) (Figure 3A). Multivariable analysis based on the Andersen-Gill model including time-dependent postremission strategy, as well as pretreatment values (Table 1) of white blood cells, platelets, bone marrow (BM)-blast percentage, age, and karyotype (normal vs abnormal) revealed that alloHSCT (hazard ratio [HR] 0.23; \( P < .001 \)) and autoHSCT (HR 0.37; \( P = .012 \)) applied in CR1 independently had a favorable prognostic impact regarding RFS (Table 3). However, apparently due to a high second CR rate after salvage therapy, the superior RFS after alloHSCT and autoHSCT did not translate into a better OS in univariable analysis (\( P = .12 \)) (Figure 3B) and multivariable analyses (Table 4).

In 45 relapsed patients, OS measured from the date of relapse was 46% (95% CI, 30-60) after 3 years (Figure 4). All patients surviving more than 2 years after having first relapsed had undergone an alloHSCT (\( n = 15 \), Figure 4).
time-to-treatment bias again by including important pretreatment characteristics.

By using methods that adjust for the time from CR to consolidation, we were able to show a clear superior RFS (P < .001) in patients who received an alloHSCT or an autoHSCT in CR1 of 73% (95% CI, 54-86) and 60% (95% CI, 33-79) after 5 years, respectively. These survival rates compare favorably to the RFS of 32% (95% CI, 21-45) in patients receiving intensive chemotherapy only. A similarly good outcome has also been reported for other AML entities categorized into the favorable ELN risk group, such as core binding factor AML (CBF-AML), including AML with inv(16) or t(16;16) and AML with t(8;21) after both alloHSCT and autoHSCT. However, our results suggest that RFS after intensive chemotherapy is substantially lower for AML with CEBPAdm as compared with that of CBF-AML. Nevertheless, due to a high second CR rate in relinduced relapsed patients with more than 80% and a high proportion of patients proceeding to an alloHSCT after relapse, the high relapse rate in the chemotherapy subgroup did not translate into a significant inferior OS. In fact, the high second CR rate and favorable survival after relapse observed in the study reported here are comparable to the survival probabilities observed in AML with inv(16). Based on these data, AML with CEBPAdm and AML with inv(16) or t(16;16) appear as 2 well-defined exceptions from the general notion that after relapse a second CR is rarely achieved. Therefore, instead of applying alloHSCT as the compelling option in CR1, an alternative and not unreasonable strategy would be to postpone the alloHSCT in CR1 and keep the option of alloHSCT for salvage for the restricted fraction of patients after relapse. Indeed, our data supports both strategies, alloHSCT or autoHSCT in CR vs intensive chemotherapy as consolidation in CR1, and reinduction followed by alloHSCT in case of relapse. Of note, the good results in our study with autoHSCT are paralleled by those obtained in the core-binding factor AML, indicating a specific chemosensitivity of these AMLs with favorable risk according to the ELN recommendations to dose escalation during consolidation therapy in CR1. Patients have to be well informed about the risks and consequences of alloHSCT and autoHSCT in CR1 regarding (1) short-term and long-term physical and psychological impairment; (2) infertility and a higher rate of treatment-related mortality (eg, for alloHSCT, we observed 24% at 5 years in our cohort); and (3) increased rates of transplantation-related morbidity and mortality for alloHSCT when the latter is performed after relapse. Besides the survival considerations, there are other various arguments that would favor the choice of an autoHSCT in CR1 as compared with alloHSCT. Given the nearly identical RFS and OS rates after alloHSCT and autoHSCT, the focus of outcome evaluations can be broadened to consider quality of life aspects and late effects after transplantation, as well as health economics, with a significantly better quality of life and

Table 3. Andersen-Gill model for the endpoint RFS

<table>
<thead>
<tr>
<th>Prognostic markers</th>
<th>RFS</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>0.23</td>
<td>0.11-0.51</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Autologous HSCT</td>
<td>0.37</td>
<td>0.17-0.80</td>
<td>.012</td>
</tr>
<tr>
<td>Log10(WBC)</td>
<td>1.40</td>
<td>0.77-2.56</td>
<td>.27</td>
</tr>
<tr>
<td>Log10(platelets)</td>
<td>0.81</td>
<td>0.40-1.66</td>
<td>.57</td>
</tr>
<tr>
<td>% BM blasts (10%)</td>
<td>0.94</td>
<td>0.82-1.08</td>
<td>.40</td>
</tr>
<tr>
<td>Age (difference of 10 y)</td>
<td>0.86</td>
<td>0.68-1.08</td>
<td>.20</td>
</tr>
<tr>
<td>Abnormal karyotype</td>
<td>0.73</td>
<td>0.38-1.40</td>
<td>.35</td>
</tr>
</tbody>
</table>

WBC, white blood cell count.

In recent years, it has become apparent that the favorable prognosis of CEBPAdm gene mutations largely depends on the presence of the CEBPAdm mutation type. At the molecular level AML with the CEBPAdm compared with AML with CEBPA single mutation type is associated with a lower frequency of coexisting NPM1 mutations and FLT3 internal tandem duplications. Therefore, several investigators have recently suggested restricting the provisional WHO 2008 entity AML with CEBPA mutations to those with biallelic mutations. As a direct consequence, the incidence of this AML entity defined by CEBPAdm decreases by about 40% to a frequency of 3% to 6% of all AML cases. The low frequency of CEBPAdm explains why comparative analyses with regard to different postremission strategies, such as alloHSCT, autoHSCT, and intensive chemotherapy, have not been performed so far. Beside the recommended ELN risk category AML with CEBPA, we also included the group of intermediate-risk karyotypes into the analyses that includes approximately 30% of patients with chromosomal abnormalities, in particular interstitial deletion 9q28 and 11q (Table 2) instead of only patients with AML exhibiting a normal karyotype. This approach is supported by the similar favorable outcome in AML with CEBPAdm with and without normal karyotype in univariable and multivariable analyses presented here (Figure 2). Thus, these data add evidence that AML with CEBPAdm may be regarded as a distinctive AML entity irrespective of additional chromosomal abnormalities categorized within the cytogenetically defined intermediate-risk group.

In the current analyses, we started with a total cohort of 5724 patients from which 5147 had a karyotype and, of those, the CEBPAdm status in 2983 was available. This large cohort was required to finally achieve a sufficiently high number of 124 AML patients with CEBPAdm in CR1 representing the basis of our analyses. This approach underlines that large cooperative intergroup meta-analyses are warranted to evaluate treatment effects with acceptable statistical power in rare but clinically, highly relevant patient subsets.

Our patients were treated in 7 different treatment trials, in part, with changing therapeutic concepts over time. Thus, it is impossible to apply the rigorous statistical standards for postremission treatment allocation such as up-front or the so-called genetic randomization. Instead, we applied statistical methods that have all in common, that group allocation is implemented as a dynamic process over time with a transition from the no-transplant group to the alloHSCT or autoHSCT groups at the time point of HSCT. This approach reduces the time-to-treatment bias and provides a solid statistical methodology in situations in which simple Kaplan-Meier plots and log-rank tests, as well as simple Cox regression models, are no longer valid. However, to further reduce selection bias toward HSCT in CR1, our univariable comparisons were complemented by multivariable Andersen-Gill regression models addressing the

Table 4. Andersen-Gill model for the endpoint OS

<table>
<thead>
<tr>
<th>Prognostic markers</th>
<th>RFS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95%-CI</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>0.50</td>
<td>0.21-1.17</td>
<td>.11</td>
</tr>
<tr>
<td>Autologous HSCT</td>
<td>0.57</td>
<td>0.23-1.40</td>
<td>.22</td>
</tr>
<tr>
<td>Log10(WBC)</td>
<td>1.34</td>
<td>0.64-2.80</td>
<td>.44</td>
</tr>
<tr>
<td>Log10(platelets)</td>
<td>0.95</td>
<td>0.40-2.26</td>
<td>.91</td>
</tr>
<tr>
<td>% BM blasts (10%)</td>
<td>1.04</td>
<td>0.87-1.24</td>
<td>.69</td>
</tr>
<tr>
<td>Age (difference of 10 y)</td>
<td>1.08</td>
<td>0.82-1.42</td>
<td>.59</td>
</tr>
<tr>
<td>Abnormal karyotype</td>
<td>1.14</td>
<td>0.55-2.34</td>
<td>.73</td>
</tr>
</tbody>
</table>

WBC, white blood cell count.
fewer late effects after autoHSCT compared with alloHSCT, whereas data on health economics are very system specific.

In summary, our data provide novel clinical information that may be useful for refining the WHO 2008 classification and the ELN risk categorization for the provisional entity AML with CEBPAdm in that beyond normal karyotype, in all intermediate-risk cytogenetics should be included. From a clinical perspective alloHSCT and autoHSCT performed in CR1 were associated with comparatively excellent RFS and OS, whereas the reduced rate of RFS in patients receiving consolidation with intensive chemotherapy could be made up after relapse by a high rate of second CR followed by alloHSCT. Thus, the marker CEBPAdm develops with respect to RFS to a predictive marker indicating superior RFS after autoHSCT and alloHSCT, but remains a prognostic marker with respect to OS. The pros and cons of alloHSCT and autoHSCT during CR1 or, as an alternative option, alloHSCT after relapse, have to be carefully considered and discussed with the patients with possible individual adaptation of treatment recommendations while taking into account the patient’s personal context.

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Authorship


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The value of allogeneic and autologous hematopoietic stem cell transplantation in prognostically favorable acute myeloid leukemia with double mutant *CEBPA*