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The prognostic significance of early treatment response in pediatric relapsed acute myeloid leukemia: Results of the international study Relapsed AML 2001/01

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Abstract

The prognostic significance of early response to treatment has not been reported in relapsed pediatric akute myeloid leukemia. In order to identify an early and easily applicable prognostic factor allowing subsequent treatment modifications, we assessed leukemic blast counts in the bone marrow by morphology on days 15 and 28 after first reinduction in 338 patients of the international Relapsed-AML2001/01 trial. Both day 15 and day 28 status was classified as good (≤20% leukemic blasts) in 77% of patients. The correlation between day 15 and 28 blast percentages was significant, but not strong (spearman-correlation-coefficient=0.49, p<0.001). Survival probability decreased in a stepwise fashion along with rising blast counts at day 28. Patients with ≤5% compared to those with blast counts of 6-10%, 11-20% and >20% had a 4-year p-survival of 52%±3% vs. 36%±10% vs. 21%±9% vs. 14%±4%, respectively, p<0.0001, which trend was not seen for day 15 results. Multivariate analysis showed early treatment response at day 28 to be of the strongest prognostic significance, superseding even time to relapse (< or ≥12 months). In conclusion, an early response to treatment, measured on day 28, is a strong and independent prognostic factor potentially useful for treatment stratification in pediatric relapsed akute myeloid leukemia. This study was registered with ISRCTN code: 94206677
Introduction

Survival of children after a relapse of AML is generally poor\textsuperscript{1,2} but has improved for several groups during the last 20 years along with better treatment approaches.\textsuperscript{3-7} The most recently published study reported a probability of survival after relapse of only 38\% at 4 years.\textsuperscript{8} In general, patients with relapse are currently treated with very intensive reinduction chemotherapy followed by hematopoietic stem cell transplantation (HSCT) from either a related or unrelated donor.\textsuperscript{3,6}

Until now the time to relapse or the duration of first complete remission (CR1) has been considered the most important prognostic factors for outcome after relapse in pediatric AML.\textsuperscript{6,9,10} The 3-5-year survival rates are reported to be in the range of only 10 to 28\% in early relapse (relapse occurring within 12 – 18 months from diagnosis) compared to 40-48\% in late relapses.\textsuperscript{7,8,10} Other factors described to be prognostic in the relapse setting are French-American-British (FAB) subtypes, cytogenetics and intensity of first-line treatment, particularly with or without allogeneic HSCT.\textsuperscript{5-7}

A good early treatment response in newly diagnosed AML, whether assessed morphologically, molecularly or by immunophenotyping, is accepted as a favorable prognostic indicator, but the significance of early response in relapsed AML in children has not previously been studied. Our aim was, to compare the prognostic significance of early treatment response at day 15 and day 28 in order to identify those patients who have only minimal chances of cure with current (standard) relapse therapy. This was studied within the international trial Relapsed AML 2001/01.\textsuperscript{8}

Methods

The prospective international study Relapsed AML 2001/01 enrolled 568 patients (515 patients with first relapse and 53 primary refractory AML patients), below <21 years of age, from 11/2001 – 4/2009 from 13 study groups.\textsuperscript{8} Patients with acute promyelocytic leukemia and myeloid leukemia in Down syndrome were not included. This analysis was based on 546 patients, because 22 patients with isolated extramedullary relapse were excluded.
Early treatment response was evaluated microscopically by bone marrow (BM) blast percentage on day 15 and day 28 of first reinduction (for details see online supplement). The core group for this analysis consisted of 338 patients with data on BM examinations on both day 15 and 28. Day 15 BM findings did not influence subsequent therapy, whilst patients with more than 20% blasts on day 28 were off-protocol and eligible for more experimental or even palliative therapy.

The human investigations were performed after approval by all local ethical committees and by the departments of Health and Human Services and in accordance with the declaration of Helsinki (ISRCTN code: 94206677).

Treatment

Reinduction therapy with Fludarabine, cytarabine, and G-CSF (FLAG) was randomized against FLAG plus liposomal daunorubicin (L-DNR/FLAG) in 1st reinduction. L-DNR (DaunoXome®, DNX) was chosen because of its potentially low cardiotoxicity (for details see8). Second reinduction for all patients was scheduled with FLAG. In patients with \( \leq 20\% \) blasts on day 28 consolidation with cytarabine and etoposide or thioguanine and cytarabine was given to bridge the time until HSCT. Patients with \( >20\% \) blasts on day 28 were “off study” and could receive new therapy options.

Definitions and statistics

Definitions: Second complete remission (CR2) = \( \leq 5\% \) leukemic blasts in BM, regeneration of the peripheral blood count (platelets \( >50\times10^9/l \), neutrophils \( >1.0\times10^9/l \)), no leukemic blasts. Primary refractory disease = failure to achieve CR in newly diagnosed AML. Relapse = recurrence of \( \geq 10\% \) unequivocal leukemic cells in BM, and/or leukemic infiltrations at any site after CR1. Early relapse = relapse within 1 year, late relapse = \( \geq 1 \) year from initial diagnosis. Poor early treatment response = BM blast count of \( >20\% \) after induction (on day 15 or day 28). Morphological favorable subgroups = FAB M1/2 with Auer rods and M4eo,11 favorable cytogenetics = \( t(8;21) \) or inv(16).

Statistics: Primary endpoint of the study was the day 28 BM status. Secondary endpoints were day 15 BM status, CR2 and long-term survival. Survival (OS) was defined as time to death or last follow-up. The Kaplan-Meier method was used to estimate survival rates, differences were compared with the 2-sided log-rank test. Differences in proportions were assessed by the chi square test. The Cox
proportional hazards model was used for uni- and multivariate analyses. P-values ≤ 0.05 were considered statistically significant, and if > 0.05 but ≤ 0.10 of borderline statistical significance. Results are presented as estimated probability of 4-year pOS with standard error (± SE). All living patients were censored at time of last follow-up, but no later than January 1, 2011.

Results

Patient characteristics

Out of 496 patients with data on day 28, 338 patients had data on both day 15 and day 28. Comparing this core-group of 338 patients with all others (n=208), the latter cohort contained fewer patients with favorable cytogenetics (p=0.01) or favorable morphology (p=0.01), and less patients with a late relapse (p<0.001) or younger age p<0.001). White blood cell (WBC) counts were not different between these cohorts (see supplementary Table S1).

The survival rates were inferior in the 208 patients without data on both time points compared to the core-group (4-year pOS 30%±3% vs. 41% ±3%, plogrank0.0003). This difference can be partially explained by the fact that patients who died early could not be evaluated on day 15 and day 28.

Table 1 shows the characteristics of the core-cohort (n=338) with data on day 15 and day 28 BM status. Subgroups of patients with favorable morphology and favorable cytogenetics more often had ≤20% blasts on day 15 (p=0.001 and p=0.0001, respectively) and on day 28 (p=0.0001 and p≤0.00001, respectively). Only 2/71 (3%) patients with favorable cytogenetics presented with ≥20% blasts on day 28 compared to 69/240 (29%) patients with other cytogenetic findings.

Whereas the treatment response measured on day 15 did not clearly differ between patients according to time to relapse (early relapse ≥20% blasts, n=39/146 [27%] vs. late relapse n= 36/170 [21%] p=0.28), significantly more patients with an early relapse (n=47/146, 32%) had a poor treatment response on day 28 compared to those with late relapse (n=24/170, 14%, p=0.00017).
Correlation between the BM blast counts on day 15 and 28

Table 2 shows the correlation between the BM day 15 and day 28 blast counts in patients with data at both time points. Remarkably few patients were allocated to the subgroups with 6-10% and 11-20% blasts at both time points. The blast percentages on day 15 and day 28 correlated significantly, but not very strongly (spearman correlation coefficient = 0.49, p < 0.001). The majority of patients with ≤20% blasts on day 15 (n=261) also had ≤20% blasts on day 28 (231/261 = 89%, see Table 2). However, 30 out of 77 (39%) patients with >20% blasts on day 15 had ≤20% blasts on day 28. These 30 patients had a better outcome than the remaining 47 patients (see below). But only 22 of the 77 patients (21%) with > 20% blasts on day 28 had < 5% blasts on day 15.

Outcome in patients according to response on day 15 and/or day 28

Seventy-seven percent of the 338 core-group patients showed a favorable reinduction response (≤20% blasts) both on day 15 and day 28. Overall, the 4-year survival in these core-group patients was 41% ± 3%. There were clear differences in survival rates between good and poor responders at both time-points (day 15: 47% ± 3% vs. 21 ± 5%, day 28: 48% ± 3% vs. 14% ± 4%), showing a trend towards even worse outcome in poor responders at day 28. Interestingly, whilst the survival rates were similar in the subgroups with blast counts 0-5%, 6-10% and 11-20% on the day 15 BM (Figure 1), there was a significant, stepwise trend to worsening survival with the categories of increasing blast counts at day 28 (Figure 2) indicating that the day 28 is a more fine-tuned and reliable predictor of survival (Table 3). When combining the BM data from day 15 and day 28 (Figure 3), the combination “day 15 >20% blasts” but “day 28 ≤20% blasts” indicated an intermediate survival probability after relapse, while patients with ≤20% blasts on both day 15 and day 28 showed a favorable survival rate, and patients with >20% blasts on day 28 faced a very poor outcome regardless of the day 15 BM result.

Results according to achievement of second remission

One-hundred-five patients of the core-group did not achieve CR2 (4-year survival 13% ± 3%) and 233 patients did (4-year survival 53% ± 3%, \( p_{(logrank)} \leq 0.0001 \)). Patients with a poor early treatment response on day 15 had a CR2 rate of 35%, whilst it was extremely low (10%) in those with a poor
response based on day 28. CR2 rates mirrored survival rates in that they fell proportionately with an increasing blast count on day 28 rather than with the 15 day blast count (Table 3).

**Early treatment response in relation to the time to relapse**

Early treatment response appeared to have stronger prognostic significance than time to relapse, since patients with either an early or a late relapse and day 28 BM blasts of ≤20% had only a slightly different, relatively favorable survival rate (4-year pOS 41%± 5% and 55% ± 4%, respectively, p=0.05). Likewise, survival of patients with day 28 BM blasts >20% was poor in both early and late relapses with a 4-year pOS 8% ± 4% and 25% ± 9%, p=0.02, respectively (Figure 4). However, it has to be mentioned that a larger proportion of those with late relapse had a good response compared to those with early relapse (86% vs. 68%, p<0.001).

**Multivariate analysis**

In a model combining time to relapse (early vs. late) and BM status on days 15 and day 28 (poor vs. good), early treatment response as determined on day 28 was the strongest independent prognostic factor. In a Cox regression analysis of survival adding cytogenetics, favorable cytogenetics was a strong prognostic factor (risk ratio 0.4, 95%-C.I. 0.2-0.6, p<0.001), BM day 15 blast count lost statistical significance (risk ratio 1.2, p=0.43), and BM blast count at day 28 of >20 % (risk ratio 2.5, 95%-C.I. 1.6-4.0, p<0.001) and early relapse (risk ratio 1.6, 95%-C.I. 1.2-2.3, p=0.005) each independently predicted poor outcome after relapse.

The prognostic value of blast count was independent of the treatment effect. There was no significant interaction between treatment effect (FLAG only vs L-DNR/FLAG) and day 15 (p=0.3) or day 28 blast count (p=0.4).

**Comparison of day 28 data based on morphology and immunophenotyping**

In a limited subset of 20 patients including several samples with an uncertain morphological result at day 28 we piloted parallel assessment also by immunophenotyping (for technical aspects including the antibody panel see12).
In 8 patients blasts had been suspected by morphology, of which six were confirmed and two were found not evaluable by immunophenotyping due to poor material. Out of 12 patients with no blasts by morphology, seven were also negative by immunophenotyping, four patients presented with 1-2% blasts and one patient with 20% blasts by immunophenotyping.

**Discussion**
Prognostic factors at diagnosis and relapse are most useful if they influence treatment decisions.
Whilst no subgroup has a sufficiently favorable outcome to justify treatment reduction, intensive AML reinduction therapy currently leaves little room for treatment intensification. However, this may change upon the introduction of novel drugs and treatment modalities. Moreover, the identification of a subgroup with minimal chances of cure may result in palliative or more experimental therapy.

Response to induction chemotherapy is a well-known prognostic factor in *de novo* AML. However, the prognostic value of early treatment response in the setting of pediatric relapsed AML has not previously been reported. According to our results, the day 28 BM status is a strong and independent prognostic factor, allowing an even better discrimination into two risk groups than the time to relapse, which until now is generally considered to be the most important risk factor. In this study, patients with an early relapse but a good early treatment response on day 28, which was observed in 68% of them, had long-term outcome which was only slightly inferior (p=0.05) to patients with late relapse and a good early treatment response (Figure 4).

After relapse >20% blasts at day 15 and day 28 is much commoner (23% patients) than in *de novo* AML (as compared with e.g. day 15 data from study AML-BFM 2004: N=37 of 499, 7%, p<0.001), indicating increased resistance to chemotherapy at relapse as compared to *de novo* AML.

Relapse “per se” is the highest risk factor for survival and there is no definable group with relapsed AML which has an outcome sufficiently favorable to consider treatment reduction. Indeed, late relapses with a good early treatment response, only had a probability of overall survival at 4 years of 55%. Our main aim was thus to identify a group of patients for which a poor survival can be predicted.
early and reliably. This group of patients with an estimated survival rate below 10-20% could be a
target for experimental therapy, e.g. treatment in phase I or II studies for new agents or new HSCT
approaches, or even palliation only.

Day 28 blast count was already the primary endpoint comparing FLAG or L-DNR/FLAG in study
Relapsed AML 2001/01. The percentage of patients with >20% blasts on day 28 was 10% lower with
L-DNR/FLAG compared to FLAG only, and the CR2 rate was similarly higher with L-DNR/FLAG,
which thus improved the early response rate significantly. This did not translate into better survival
rates in the L-DNR/FLAG group, which may be related to cross-over effects with more treatment
intensifications especially in poor responders. However, this study now shows that the prognostic
value of the day 28 blast count is not influenced by the treatment effect of L-DNR.

The percentage of patients with a BM blast count of \( \leq 20\% \) on days 15 and 28 was similar at 77%.
Likewise, the gaps between 4-years survival rates of patients with \( \leq 20\% \) and > 20% blasts at day 15
and day 28 were almost similar. However, in contrast to the BM day 15 data which did not
discriminate between different survival rates in subgroups by blast count (0-5%, 6-10%, 11-20%),
there was a clear and significant trend to worse survival with increasing BM blast counts at day 28.
Thirty nine percent of patients with a day 15 BM containing >20% blasts had a day 28 BM with \( \leq 20\% \)
blasts, and this conversion from poor to good early treatment responder was associated with a better
outcome (Figure 3). This may be explained by the fact that the usually aplastic day 15 BM may still
contain residual but non-proliferating leukemic blasts which are bound to subsequent disappearance
upon delayed drug-action or to subsequent superimposition by normal regeneration. Conversely, on
day 28 normal hematopoiesis is recovering and truly resistant leukemic blasts could regrow together
with normal progenitors. In this situation and especially in patients with \( \leq 20\% \) blasts on day 15, but
with >20% blasts on day 28 (n=30, 14% of patients) concurrent regeneration of both leukemic blasts
and normal progenitors may hamper correct assessment by conventional morphologic methods.
Obviously, additional methodology like immunophenotyping and/or genetic investigations could then
be of relevant discriminative value.14-16
Achievement of remission after relapse (CR2) is essential for long term survival. But the time point of eventual CR2 (according to the classical definition of both BM and peripheral blood parameters) may vary considerably because post-induction treatment of AML is often continued before all regeneration parameters needed to fulfill CR criteria are reached. Therefore, from a clinical point of view assessment of classical CR will not allow timely treatment modifications.

By multivariate analysis, favorable cytogenetics (23% of relapsed patients) was a strong favorable prognostic factor: only 2 of 71 patients presented with >20% blast on day 28, and 64 patients had a blast count ≤5%. For the majority of patients, early treatment response on day 28 was the strongest prognostic factor, which at least partly superseded also the time to relapse.

Hence, microscopic early response assessment – even in an internationally collaborative trial involving many sites - is an overriding prognostic factor in pediatric relapsed AML which is robust enough to discriminate between subgroups with significantly different probabilities of CR2 and of overall survival. This is of high relevance for the design of upcoming trials because it allows for early treatment modifications in selected patient cohorts. Moreover, microscopic evaluation is usually available in centers dedicated to care of children with leukemia even in case of limited economic or technical resources.

Nevertheless, we are aware that morphologic assessment has limitations. First of all, investigator experience is essential and even then, it remains a subjective method. A well-known problem is the discrimination between normal blasts occurring with hyper-regeneration of progenitors and leukemic blasts after aplasia. Also, low numbers of leukemic blasts can be overlooked. In such situations, other diagnostic methods like immunophenotyping can render additional information or proof of cellular dignity. In a small and selected patient group of our study, there was a good concordance between blast counts evaluated by morphology and immunophenotyping, but immunophenotyping was superior in evidencing leukemic cells at counts <5% as well as even in one occasional case with 20% blasts which were misinterpreted by morphology as normal. False-positivity of morphological findings was not an issue in this cohort. Notably, immunophenotyping results were experimental and not used for clinical decisions.
In summary, the microscopic day 28 BM blast count is a strong and independent prognostic factor in pediatric relapsed AML. It has better discriminative value than the time to relapse or the day 15 BM status. Treatment evaluation on day 28 of therapy still allows treatment modifications, which might eventually allow improving the poor outcome that patients with >20% leukemic blasts at that time-point currently face. Additional techniques such as multicolor immunophenotyping are likely to improve the discrimination between normal and leukemic blasts at early time-points, and may add benefit to risk-group adapted therapy in pediatric relapsed AML.

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Authorship

Contributions: All co-authors were involved in the design of the study. GJK, MZ, RT, BG and UC wrote the study protocol and MZ, UC and GJK performed the data analysis. All investigators were involved in study design, data collection and data interpretation, reviewed manuscript drafts and approved the final manuscript; UC and GJK wrote the initial manuscript draft and vouches for the data, analysis, and manuscript submission.
Conflict of Interest Disclosure: DR and GJK are members of the advisory board from Galen. The other authors declare no competing financial interests.

References


Table 1: Patient characteristics of the cohorts with ≤/≥ 20% BM blasts on day 15 and day 28

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</tbody>
</table>

Medians are given for continuous variables and absolute numbers for categorical values. FAB-type = French American British type, BM = bone marrow

Bold indicates significant p-values

*Data were not available in all 338 patients: Leukocytes at relapse, n = 325; FAB at relapse n = 316; cytogenetics at relapse n = 307.
Table 2: Correlation between the BM blast counts on day 15 and 28

<table>
<thead>
<tr>
<th>Row Pct</th>
<th>BM day 15 0-5</th>
<th>BM day 15 6-10</th>
<th>BM day 15 11-20</th>
<th>BM day 15 &gt; 20</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM day 15 0-5%</td>
<td>173</td>
<td>11</td>
<td>7</td>
<td>22</td>
<td>213</td>
</tr>
<tr>
<td>BM day 15 6-10%</td>
<td>13</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>BM day 15 11-20%</td>
<td>18</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>BM day 15 &gt; 20%</td>
<td>16</td>
<td>4</td>
<td>10</td>
<td>47</td>
<td>77</td>
</tr>
<tr>
<td>Total</td>
<td>220</td>
<td>22</td>
<td>19</td>
<td>77</td>
<td>338</td>
</tr>
</tbody>
</table>

BM = bone marrow

Table 3: Summary of CR2 achievement and 4-year survival results according to day 15 and day 28 BM blasts counts

<table>
<thead>
<tr>
<th>BM blasts</th>
<th>BM day 15</th>
<th>BM day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>N CR2 N (%) pOS (SE) in %</td>
<td>N CR2 N (%) pOS (SE) in %</td>
</tr>
<tr>
<td>0-5</td>
<td>213 174 (82) 46 (4)</td>
<td>223 203 (92) 52 (4)</td>
</tr>
<tr>
<td>6-10</td>
<td>19 12 (63) 52 (12) 23 10 (46) 35 (10)</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>29 20 (69) 47 (9) 19 12 (63) 21 (9)</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>77 27 (35) 21 (5) 77 8 (10) 14 (4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>338 233 (69) 41(3)</td>
<td>338 233 (69) 41(3)</td>
</tr>
</tbody>
</table>

CR2 = second complete remission, BM = bone marrow

Bold indicates the better discrimination on BM day 28 compared to BM day 15
Figure Legends

**Figure 1.** Probability of 4-year survival after relapse according to blast counts at day 15. SE = standard error, \( p_{(logrank)} \) 0-5 vs. \( >20 <0.0001; 6-10 vs. >20 \sim 0.011; 11-20 vs. >20 \sim 0.0011; \) all other comparisons \( >0.68. \)

**Figure 2.** Probability of 4-year survival after relapse according to blast counts at day 28. SE = standard error, \( p_{(logrank)} \) 0-5 vs. 11-20 \( \sim 0.0010; 0-5 vs. >20 <0.0001; 6-10 vs. >20 \sim 0.0031; \) all other comparisons \( >0.15. \)

**Figure 3.** Probability of 4-year survival after relapse combining blast count data at day 15 and day 28. SE = standard error, \( p_{(logrank)} \) BM day 15 \( \leq 20 \) and day 28 \( \leq 20 \) vs. BM day 15 \( \leq 20 \) and day 28 \( >20 <0.0001; \) BM day 15 \( \leq 20 \) and day 28 \( \leq 20 \) vs. BM day 15 \( >20 \) and day 28 \( >20 <0.0001; \) BM day 15 \( \leq 20 \) and day 28 \( >20 \) vs. BM day 15 \( >20 \) and day 28 \( >20 <0.0001; \) late relapse and BM day 28 \( \leq 20 \) vs. early relapse and BM day 28 \( \leq 20 \sim 0.05; \) late relapse and BM day 28 \( \leq 20 \) vs. early relapse and BM day 28 \( >20 <0.0001; \) late relapse and BM day 28 \( >20 \) vs. early relapse and BM day 28 \( >20 \sim 0.028; \) late relapse and BM day 28 \( >20 \) vs. early relapse and BM day 28 \( >20 <0.0001. \)

**Figure 4.** Probability of 4-year survival after relapse according to time of relapse and blast count at day 28. SE = standard error, \( p_{(logrank)} \) late relapse and BM day 28 \( \leq 20 \) vs. late relapse and BM day 28 \( >20 <0.0004; \) late relapse and BM day 28 \( \leq 20 \) vs. early relapse and BM day 28 \( \leq 20 \sim 0.05; \) late relapse and BM day 28 \( \leq 20 \) vs. early relapse and BM day 28 \( >20 <0.0001; \) late relapse and BM day 28 \( >20 \) vs. early relapse and BM day 28 \( >20 \sim 0.022; \) early relapse and BM day 28 \( \leq 20 \) vs. early relapse and BM day 28 \( >20 <0.0001. \)
BM 15 0-5  0.46, SE=0.04 (N=213, 113 events)
BM 15 6-10  0.52, SE=0.12 (N=19, 9 events)
BM 15 11-20  0.47, SE=0.09 (N=29, 15 events)
BM 15>20   0.21, SE=0.05 (N=77, 63 events)
Supplementary information

Supplemental Methods

Early treatment response was evaluated on the basis of the bone marrow (BM) blast percentage among nucleated cells determined by microscopic evaluation of conventionally stained smear preparations. These were obtained on day 15 of first reinduction and before starting the second reinduction course, which was scheduled on day 28. If the second chemotherapy course had to be postponed, because of prolonged aplasia or severe infection, BM was obtained as soon as possible thereafter (between day 28 and day 42 from start of the 1st course), and the date of that evaluation was still classified as day 28. As the day 28 BM blast count was the primary endpoint also for the randomized trial question, more data were available for day 28 (n = 496) than for BM blasts on day 15 (n = 370). Thus, day 28 data were only lacking in 50 patients of the total cohort (due to early death before day 28 in 11 patients). Day 15 data might allow even earlier treatment adaptations and therefore were investigated as well in comparison to the day 28 results.
Supplementary Table S1: Patient characteristics of the cohort with missing data on day 15 or day 28 (N=208) and in the core group of patients with data both on day 15 and day 28 (N=338)

<table>
<thead>
<tr>
<th>Core Group</th>
<th>Day 15 and 28 data available</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>N</td>
</tr>
<tr>
<td>Number of patients</td>
<td>208</td>
<td>338</td>
</tr>
<tr>
<td>Age at relapse (years) median</td>
<td>6.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Leukocytes at relapse* (x10³/µl) median</td>
<td>3,100</td>
<td>3,710</td>
</tr>
<tr>
<td>(Q1-Q3)</td>
<td>2,000-12,000</td>
<td>2,180-8,000</td>
</tr>
<tr>
<td>Time to relapse (years) median</td>
<td>0.75</td>
<td>1.01</td>
</tr>
<tr>
<td>(Q1-Q3)</td>
<td>0.5-1.2</td>
<td>0.7-1.5</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>128</td>
<td>62</td>
</tr>
<tr>
<td>FAB types*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1/M2 Auer, M4eo</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Other</td>
<td>125</td>
<td>79</td>
</tr>
<tr>
<td>Cytogenetic data*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(8;21), inv(16)</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>144</td>
<td>87</td>
</tr>
<tr>
<td>Site of relapse*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM isolated</td>
<td>149</td>
<td>86</td>
</tr>
<tr>
<td>BM combined</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Early/late relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse &lt; 1 year from diagnosis</td>
<td>104</td>
<td>50</td>
</tr>
<tr>
<td>Relapse ≥ 1 year from diagnosis</td>
<td>71</td>
<td>34</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>33</td>
<td>16</td>
</tr>
</tbody>
</table>

*Data were not available in all patients