The impact of early versus late platelet and neutrophil recovery after induction chemotherapy on survival outcomes of patients with acute myeloid leukemia

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Abstract

Background and Aim: The prognosis of patients with acute myeloid leukemia (AML) is affected from the factors that are both patient and disease specific. The aim of this study is to evaluate the impact of early versus late platelet and neutrophil recovery after induction chemotherapy on survival outcomes of acute myeloid leukemia patients.

Materials and Methods: One hundred and eighty one patients with AML who were treated in our tertiary center between the years of 2001 and 2018 were evaluated. Neutrophil (NRT) and platelet recovery times (PRT) were accepted as the periods from the beginning of induction chemotherapy to a neutrophil count ≥0.5×10⁹/L and a platelet count ≥20×10⁹/L, 3 days in a row, respectively. The median time of platelet recovery was 25 day (12-52) for all patients. Therefore, in the first 25 days platelet recovery was defined as early platelet recovery (EPR) and ≥26 days was defined as late platelet recovery (LPR). The median time to neutrophil...
recovery was 28 day (13-51) for all patients. Therefore, in the first 28 days neutrophil recovery was defined as early neutrophil recovery (ENR) and ≥29 days was defined as late neutrophil recovery (LNR).

**Results:** The 5-year OS for patients who had EPR and who had LPR after induction chemotherapy were 62% and 23%, respectively (p<0.001). The 5-year DFS for patients who had EPR and who had LPR after induction chemotherapy were 57% and 15%, respectively (p<0.001).

**Conclusion:** In conclusion, the short bone marrow recovery time may indicate a better healthy hematopoiesis/marrow capacity associated with longer OS and DFS.

**Keywords:** Acute myeloid leukemia, platelet recovery, neutrophil recovery

**Introduction**

Clinical outcome of patients with acute myeloid leukemia (AML) varies across a wide spectrum, ranging from survival of a few days to remission. Therefore, the prediction of outcome is vital for those patients (1). Prognosis of patients with AML is affected from the factors that are both patient and disease specific. The most significant disease-specific prognostic factors at the time diagnosis of AML patients are cytogenetics and molecular abnormalities (2). On the other hand, the most important patient-specific prognostic factor is age at diagnosis (3). Estimating resistance to treatment in patients with AML is extremely important for critical therapeutic decisions and follow-up of the patient (4). Very few data were defined about the association between AML prognosis and bone marrow recovery kinetics following induction chemotherapy (5-7). The aim of this study is to evaluate the impact of early versus late platelet and neutrophil recovery after induction chemotherapy on survival outcomes of AML patients.

**Materials and Methods**

**Study design and data collection**

This study has been performed in a retrospective manner. All clinical data were collected from hospital medical records. As a result of application standards of the hospitals of Hacettepe Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care.

**Patients and disease characteristics**

Neutrophil (NRT) and platelet recovery times (PRT) were accepted as the periods from the beginning of induction chemotherapy to a neutrophil count ≥0.5×10⁹/L, 3 days in a row and a platelet count ≥20×10⁹/L, 3 days in a row (without transfusion support), respectively. The median time of platelet recovery was 25 day (12-52) for all patients. Therefore, in the first 25 days platelet recovery was defined as early platelet recovery (EPR) and ≥26 days was defined as late platelet recovery (LPR). The median time to neutrophil recovery was 28 day (13-51) for all patients. Therefore, in the first 28 days neutrophil recovery was defined as early neutrophil recovery (ENR) and ≥29 days was defined as late neutrophil recovery (LNR).

In this study, the patients included were as follows: age >18 years at the time of diagnosis, patients who received first induction chemotherapy, achieved complete remission after induction chemotherapy. Patients with refractory AML and patients who were diagnosed as acute promyelocytic leukemia were not included in this study. All patients included in the
study received idarubicin (12 mg/m² IV push on each of first 3 days of treatment) and Ara-C (100 mg/m² daily as a continuous infusion for 7 days) as induction chemotherapy (8).  

**Statistical analyses**

Statistical analyses were performed using the SPSS software version 25. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk’s test) to determine whether they are normally distributed or not. Statistical comparisons were made using Chi-square for categorical data. Student t-test (for two independent samples) was used for comparison of continuous numerical data. Survival analyses were made using Kaplan-Meier test. Multivariate analysis of predictors of survival was performed using Cox regression test. Parameters with P values ≤0.10 in univariate tests were included in the multivariate analysis. P values <0.05 were considered to indicate statistical significance.

**Results**

**Patients Characteristics**

A total of 450 AML patients admitted to our hospital between 2001 and 2018 were screened for this study. Patients with refractory AML, patients who did not achieve complete remission after the first induction chemotherapy and patients who died during induction chemotherapy were not included in the study. Patient characteristics are summarized in Table 1. There were 106 (57.9%) males and 77 (42.1%) females with a median age of 44 (range, 18–69) years at diagnosis. Karyotype analyses were available for 159 patients: 6 patients (3.7%) were in favorable risk group, 101 (63.5%) patients were in the intermediate-risk group and 54 (33.9%) patients were in the adverse-risk group, according to the European Leukemia Net classification (9). The number of patients classified with Eastern Cooperative Oncology Group performance status (ECOG PS) 0, 1, 2 and 3 were 4 (2.2%), 87 (48.1%), 78 (43.1%) and 12 (6.6%), respectively (10). According to the period, LPR was seen fewer in patients between 2011-2018 than patients between 2001-2010 (p=0.01). Pre-existing MDS or secondary AML was seen more in patients with LPR than in patients with EPR (p=0.02).

There were no statistically significant differences between two groups in terms of patient’s median age (p=0.10), gender (p=0.18), cytogenetic risk groups (p=0.77) and ECOG PS (p=0.06). Mortality (66.3% vs. 30.4%, p<0.001) and relapse rate (47.2% vs 29.3% p=0.01) were higher in patients who had LPR than EPR after induction chemotherapy. Non-relapse mortality rate was higher in patients who had LPR than EPR (28.1% vs 9.8% p=0.001). Major causes of NRM were infections (20 vs 8), heart attack (3 vs 0), acute renal failure (1 vs 0) and graft vs host disease (1 vs 0) in LPR and EPR patients, respectively.

**Table 1. Baseline characteristics of AML patients**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients who had EPR</th>
<th>Patients who had LPR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% )</td>
<td>92 (50.8%)</td>
<td>89 (49.2%)</td>
<td></td>
</tr>
<tr>
<td>The median age (range), years</td>
<td>41 (19-69)</td>
<td>45 (18-68)</td>
<td>0.10</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>49/43 (53.3%/46.7%)</td>
<td>56/33 (62.9%/37.1%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Platelet recovery time±SD</td>
<td>19.8±3.4</td>
<td>35.5±7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td></td>
<td>3 (3.3%)</td>
<td>1 (1.1%)</td>
<td>52 (56.5%)</td>
</tr>
<tr>
<td></td>
<td>190</td>
<td>3</td>
<td>32 (34.8%)</td>
</tr>
<tr>
<td></td>
<td>357</td>
<td>5</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>Cytogenetic risk group</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>2 (2.2%)</td>
<td>4 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>50 (54.3%)</td>
<td>51 (57.3%)</td>
<td></td>
</tr>
<tr>
<td>Adverse</td>
<td>28 (30.4%)</td>
<td>24 (27.0%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>12 (13.0%)</td>
<td>10 (11.2%)</td>
<td></td>
</tr>
<tr>
<td>According to time period</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001-2010</td>
<td>27 (39.1%)</td>
<td>42 (60.9%)</td>
<td></td>
</tr>
<tr>
<td>2011-2018</td>
<td>65 (58 %)</td>
<td>47 (42%)</td>
<td></td>
</tr>
<tr>
<td>Pre-existing MDS or secondary AML</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing MDS</td>
<td>1 (1.1%)</td>
<td>9 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>Secondary AML</td>
<td>3 (3.3%)</td>
<td>2 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Patients who had early/late neutrophil recovery</td>
<td>77/15 (83.7%/16.3%)</td>
<td>23/66 (25.8%/74.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutrophil recovery time±SD</td>
<td>24.8±7.1</td>
<td>34.0±8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AlloHSCT</td>
<td>66 (71.7%)</td>
<td>46 (51.7%)</td>
<td></td>
</tr>
<tr>
<td>Relapse rate (%)</td>
<td>27 (29.3%)</td>
<td>42 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>Mortality rate (%)</td>
<td>28 (30.4%)</td>
<td>59 (66.3%)</td>
<td></td>
</tr>
<tr>
<td>Non-relapse mortality (%)</td>
<td>9 (9.8%)</td>
<td>25 (28.1%)</td>
<td></td>
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<tr>
<td>Abbreviations: EPR: Early platelet recovery; LPR: Late platelet recovery</td>
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</table>

**Overall Outcomes**

Median follow-up time was 21 months (range 1.5-220) for all patients. The 3-year OS for patients who had EPR and LPR were 68% and 40%, respectively. The 5-year OS for patients...
who had EPR and LPR were 62% and 23%, respectively (p<0.001). The 3-year DFS for patients who had EPR and LPR were 64% and 28%, respectively. The 5-year DFS for patients who had EPR and LPR were 57% and 15%, respectively (p<0.001).

The 3-year OS for patients who had ENR and LNR were 63% and 42%, respectively. The 5-year OS for patients who had ENR and LNR were 53% and 28%, respectively (p<0.001). The 3-year DFS for patients who had ENR and LNR were 57% and 32%, respectively. The 5-year DFS for patients who had ENR and LNR were 46% and 22%, respectively (p<0.001) (Figure 1).

Figure 1. Overall survival and disease free survival for patients (A-B for EPR and LPR group, C-D for ENR and LNR group)

**Cox regression analyses**

In univariate analyses, factors affecting OS were age (p=0.004), cytogenetics (p<0.001), ECOG PS (p<0.001), ENR (p<0.001) and EPR (p<0.001) of the patients, shown in Table 2. Cox regression analysis revealed the parameters to predict OS as cytogenetics (p<0.001), ECOG PS (p=0.001) and EPR (p=0.02) of the patients.

In univariate analyses, factors affecting DFS were age (p=0.006), sex (p=0.06), cytogenetics (p<0.001), ECOG PS (p<0.001), ENR (p=0.009) and EPR (p=0.001) of the patients. Cox regression analysis revealed the parameters to predict DFS as sex (p=0.002), cytogenetics (p<0.001), ECOG PS (p<0.001) and EPR (p=0.01) of the patients.

Table 2. Univariate and Multivariate Analyses of Overall Survival and Disease Free Survival

<table>
<thead>
<tr>
<th>Parameters for OS</th>
<th>Univariate analyses</th>
<th>Multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% confidence interval</td>
</tr>
</tbody>
</table>

5
| Parameters for OS | Age | 1.025 | 1.008-1.042 | **0.004** | 1.003 | 0.987-1.020 | 0.69 |
| Sex (female) | 0.730 | 0.470-1.132 | 0.159 |
| Cytogenetic | 2.350 | 1.770-3.120 | **<0.001** | 1.691 | 1.260-2.269 | **<0.001** |
| ECOG PS | 3.271 | 2.346-4.561 | **<0.001** | 2.393 | 1.633-3.506 | **<0.001** |
| ENR | 2.157 | 1.408-3.307 | **<0.001** | 1.337 | 0.781-2.289 | 0.28 |
| EPR | 2.744 | 1.744-4.315 | **<0.001** | 1.911 | 1.090-3.348 | **0.02** |
| Parameters for DFS | Age | 1.022 | 1.006-1.037 | **0.006** | 1.006 | 0.991-1.021 | 0.41 |
| Sex (female) | 0.678 | 0.452-1.018 | 0.06 | 0.500 | 0.324-0.772 | **0.002** |
| Cytogenetic | 2.094 | 1.625-2.698 | **<0.001** | 1.680 | 1.284-2.199 | **<0.001** |
| ECOG PS | 2.816 | 2.085-3.805 | **<0.001** | 2.392 | 1.656-3.454 | **<0.001** |
| ENR | 2.090 | 1.413-3.091 | **<0.001** | 1.281 | 0.766-2.141 | 0.34 |
| EPR | 2.650 | 1.758-3.996 | **<0.001** | 1.944 | 1.144-3.305 | **0.01** |

**Discussion**

After induction chemotherapy, the duration of neutropenia and thrombocytopenia carries risk of complications in AML patients. Some patients die from infections during neutropenic period. Intracranial hemorrhage may be seen because of thrombocytopenia as a serious life-threatening complication. In this study, EPR was one of the significant independent parameter in multivariate analysis which includes classical prognostic risk factors for OS and DFS. Since hematopoietic growth factors were used for neutrophil recovery in some patients, ENR may not have significantly resulted in long OS and DFS in multivariate analysis. Bone marrow reserve may be considered to be better in patients who had EPR and ENR. Patients with LPR and LNR may be considered more risky and donor screening may be initiated at an early stage for alloHSCT.

AML prognosis is related to bone marrow recovery, cellular kinetics (5) and blast clearance after induction chemotherapy (11, 12). Some studies reported that an early response to induction chemotherapy was to be a strong and independent prognostic factor for survival in patients with de novo and relapsed AML (13-15). Yamazaki et al. showed that the regeneration of hematopoiesis, especially the recovery of platelets, after induction chemotherapy is an important positive predictor for DFS in patients with AML (16). On the other hand, a previous study evaluated the survival outcomes of patients who underwent alloHSCT with incomplete remission (CRi, bone marrow CR with absolute neutrophil count <1,000/mm³ and/or platelet count <100,000/mm³) and complete remission (CR, bone marrow CR with absolute neutrophil count ≥1,000/mm³ and platelet count ≥100,000/mm³). The study showed equivalent posttransplant outcomes between patients who were in CR and in CRi before alloHSCT. Therefore, alloHSCT can eliminate the negative effect of pre-transplant blood count levels (17).
The major cause of NRM was infection, therefore, alloHSCT might be considered in nadir period for AML patients. However, it will be difficult to find a donor in such a short period and prepare the patient for alloHSCT.

In conclusion, early bone marrow recovery may indicate a better healthy hematopoiesis/marrow capacity associated with longer OS and DFS. As PRT and NRT are very easy to detect, they can be used as prognostic indicators in countries with limited laboratory facilities. Our results support the impression that an accelerated platelet and neutrophil recovery following chemotherapy could be accepted as a promising sign of good prognosis and thus good future response to therapy in AML. The results of this study are important for prediction of the prognosis of newly diagnosed AML patients.

Conflict of Interests

The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Role of the funding source

None.

Ethical approval: All of the ethical considerations had been strictly followed in accordance with the 1964 Helsinki declaration. As a standard care/action of the hospitals of the Hacettepe Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standard of care.

References