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Letter to the Editor

In Platelet Refractory Patients with Acute Myelogenous Leukemia, Renal Dysfunction Correlates with Shortened Survival

Amara Hussain[1], Denis Toskic[2], Cindy Varga[3], Kellie Sprague[4], Jensyn Cone Sullivan[2], Andreas Klein[2] and Raymond L Comenzo[2]*

[1]*Edward Hines Jr. VA Hospital, Hines, IL*

[2]*Tufts Medical Center, Boston, MA*

[3]*Atrium Health Levine Cancer Institute, Charlotte, NC*

[4]*Maine Medical Center, Portland, ME*

***Corresponding author**

Raymond L Comenzo, MD, Tufts Medical Center, Box 826, 800 Washington, Street Boston, MA 92111, TEL 617-636-6454, FAX 617-636-3175, USA, Email: rcomenzo@tuftsmedicalcenter.org

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TO THE EDITOR

We retrospectively examined the impact of platelet refractoriness on survival in acute myeloid leukemia (AML) patients, an occurrence that may significantly impact even fit older patients [1]. We compared platelet-refractory versus AML-control patients and learned that among AML-platelet refractory patients, renal dysfunction correlated with significantly shorter survival.

Platelet transfusions are essential in patients receiving myelosuppressive chemotherapy to minimize hemorrhage incidence; however, transfusions may provoke alloimmunization leading to refractoriness (inadequate post-transfusion count increment). Indeed, 5-15% of patients receiving chronic platelet transfusions become refractory [2].

Accepted quantitative definitions of platelet refractoriness in AML include two concurrent 1-hour post transfusion count increments of <11,000/uL or 18-24-hour post-transfusion count increments of <2,000/uL [2,3].

Platelet refractoriness etiologies are divided into immune and non-immune factors [3]. Non-immune factors prevail rather than human leukocyte antigen (HLA)-antibody or rarely human platelet antigen (HPA)-antibody immune factors [3]. Indeed, the development of such alloantibodies does not always produce immune-mediated platelet refractoriness. Immune-mediated platelet refractory patients may be treated with positively or negatively matching donor-recipient HLA antigens or cross-matching platelets. Positive donor-recipient HLA antigen matching entails transfusing donor platelets with HLA types as similar to the recipient's as possible. Unfortunately, up to 60% of such transfusions fail to increase the platelet count [4]. Negative matching, or antigen avoidance, involves administration of platelets from donors whose HLA antigens do not correspond to high-level recipient HLA antibodies. Cross-matching selects single-donor units non-reactive with recipient plasma and is suitable for recipients with either anti-HLA or –HPA antibodies. Positive and negative HLA-matched and cross match-compatible platelets are equally effective [2].

A platelet refractoriness consult service was implemented in 2010 at our medical center**.** Platelet counts and increments were recorded following consultation. Recommendations for further evaluation included a platelet cross match assay performed at the American Red Cross in Dedham, Massachusetts, HLA typing and HLA antibody testing. Pending results, patients received ABO-compatible apheresis platelet units. Subsequently, based on test results and product availability, patients received ABO-compatible, cross match-compatible or HLA-matched platelets. In this retrospective study we examined the impact of platelet refractoriness on the survival of AML patients undergoing induction therapy.

With Institution Review Board approval, we reviewed the platelet refractory consult case log from January 1, 2010-December 31, 2018 for AML patients and the electronic medical records of all patients with AML treated during that period. AML-refractory group data was gathered from seven days pre- and post-consultation, and platelet counts on the day of consultation and confirmatory increments were identified. Lifetime numbers of red blood cell (RBC) and single-donor platelet unit transfusions were calculated. Epidemiologic and clinical characteristics captured included age, gender, parity, presence of splenomegaly, body mass index, infection-related data, complete blood counts, and renal chemistries. All patients

received RBC and single-donor platelet units that were pre-storage leukodepleted and irradiated.

We used Cox regression and Kaplan Meier analyses to investigate variables associated with the development of platelet refractoriness and overall survival. The variables of interest for Cox regression analysis included age, gender, parity, BMI, renal function, primary or secondary AML, splenomegaly, ABO blood group, lifetime RBC and platelet use, exposure to vancomycin and valganciclovir, fever, infection, transfusion reaction, WHO bleeding scale, HLA alloantibody, DVT/PE, WBC/ANC/HGB and platelet counts for 7 days before and after consultation, presence of a central venous catheter, platelet cross match result, receipt of ABO-compatible or cross match-compatible or HLA-matched platelets. Cox models were programmed to identify predictors of overall survival using these variables. Overall survival was calculated from the date of diagnosis to the date of last contact or death, and in the AML-refractory group, from the date of consultation to the date of last contact. Variables of statistical significance ($p \leq 0.05$) in univariate analyses were identified. MedCalc version 19.6 (MedCalc Software, Ostend, Belgium) was used for all statistical analyses.

72 identified patients were platelet refractory between 2010-2018. Of these, 32 had AML. At consultation, the AML-refractory group had median platelet counts and increments of $7x10^9$/uL (range, 0-28) and $-2x10^9$/uL (-13-5); 14 were chronic kidney disease stage 1, 9 stage 2, 6 stage 3, 1 stage 4 and 2 stage 5. A control group with AML (n = 79) matched for age and gender to the AML-refractory group from patients treated between 2010-2018 was identified. In the AML-refractory group, 50% were compatible with all platelets tested in the platelet-cross match while HLA alloantibodies were identified in 26%. 42% were deemed non-immune refractory while 4% were immune and 16% both non-immune and immune-related refractory; in 31% (n=10) the basis for refractoriness could not be effectively determined. In the AML-refractory group, 13% had splenomegaly, 63% were being treated for possible infection and 61% were receiving vancomycin. All patients in the AML-refractory group received ABO-compatible units; 21% received cross-matched platelets and those with HLA alloantibodies received HLA-matched platelets when available. The AML-refractory group during their lifetime received median RBC and platelet units of 22.5 (1-101) and 36 (2-227) while the AML-control group received significantly fewer median RBC (10 (0-142)) and platelet units (11.5 (0-81)). The lifetime administration of blood products was greater in the AML-refractory group.

Overall survival from diagnosis was significantly longer in the AML-control versus the AML-refractory group (median 272 versus 218 days; $p < 0.01$; Figure 1A). Overall survival from consultation to death in the AML-refractory group was 59 days**.** In the AML-refractory group, only renal function achieved statistical significance for impact on survival ($p < 0.01$); those with an eGFR of ≤ 87 mL/min (the median) had a median time from consultation to death of 26 days while those with an eGFR > 87 mL/min survived a median of 150 days ($p < 0.01$) [Figure 1B].

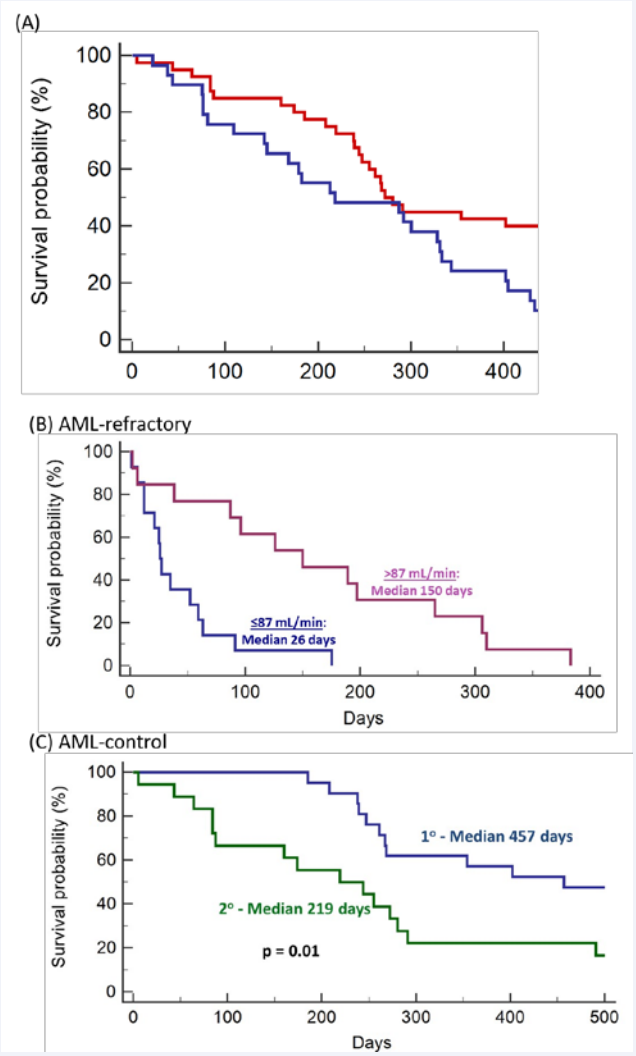

Figure 1 (A) This Kaplan-Meier curve highlights the statistically significant longer survival probability (%) from diagnosis of the AML-control group over the AML-refractory group, a median difference of 54 days.

(B) This Kaplan-Meier curve shows the only variable of interest that achieved statistical significance for impact on survival in the AML-refractory group was the renal function at time of consultation. Those with a eGFR ≤ 87 mL/min had a shorter probability of survival (%), with a median time from consultation to death of 26 days; those with a eGFR > 87 mL/min had a median time of 150 days.

(C) In the AML-control group, as expected, this Kaplan-Meier curve shows the presence of secondary AML diminished the probability of survival (%). Those with secondary AML had a survival of 219 days from time of diagnosis compared to 457 days in those with primary AML.

In the AML-control group, only the diagnosis of secondary AML significantly impacted survival from diagnosis ($p < 0.01$) [Figure 1C]; those with primary AML had longer survival than those with secondary AML (457 days versus 219 days). When comparing those with AML who were platelet refractory to those who were not, there was no difference between subtypes based on their molecular profiles (data not shown).

This report indicates that in patients with AML undergoing induction therapy platelet refractoriness frequently has a non-immune basis and that overall survival is shorter in patients with renal dysfunction, possibly linked to infection-related variables such as antibiotic use. Few studies have examined the relationship between platelet refractoriness and survival. A single-center French study retrospectively evaluated platelet refractoriness incidence and impact on survival in patients receiving intensive chemotherapy for AML. Of 897 patients, 41 (4.8%) developed platelet refractoriness [5] and had a significantly higher rate of early death from grade 3-4 bleeding than those who did not (12.2% vs. 1.4%) [5]. In addition, the overall death rate from bleeding events during therapy was substantially higher in those with platelet refractoriness (24.4% vs. 5.3%) [5].

These findings highlight the bone marrow as an organ system and thrombocytopenia and platelet refractoriness as indicators of end-organ damage. Refractory patients with declining kidney function had shorter survival and increased lifetime transfusion requirements, suggesting marrow failure increases the risk of proximal death. Moreover, renal dysfunction may amplify refractoriness by impairing platelet function. This study is limited by its single-center design and small sample sizes; nevertheless, this brief work may serve as a stepping-stone to further studies of platelet refractoriness and overall survival in AML.

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Competing Interests: There are no competing interests to declare.

Data Availability: De-identified raw data are available in XL format if requested.

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