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Implementation of a Multidisciplinary Care Pathway via an Emergency Department-ICU to Improve Care of Emergency Department Patients Presenting With Leukostasis

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Objectives: Leukostasis is a life-threatening complication of acute hyperleukocytic leukemia, and is associated with substantial mortality. Management of leukostasis requires time-sensitive diagnostics and therapeutics, and leukapheresis remains a mainstay of treatment in select patients. Leukapheresis requires coordination of multidisciplinary resources, which can prove challenging in the emergency department setting, and delays in treatment due to the complexity and coordination required are common. The objective of this study was to assess the effect of utilization of an emergency department-ICU and a multidisciplinary care pathway on outcomes of critically ill leukostasis patients presenting to the emergency department.

Design: Retrospective cohort study.

Setting: Single large academic medical center in the United States.

Patients: Adult emergency department patients with signs and symptoms of leukostasis requiring emergent leukapheresis from 2012-2019.

Interventions: Implementation of a hybrid emergency department-ICU setting (emergency critical care center) and a multidisciplinary care pathway with members from Emergency Medicine, Hematology, Blood Bank, and Clinical Pathology.

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Measurements and Main Results: A total of 70 patients were identified and included for analysis: 14 preemergency critical care center; 32 postemergency critical care center, premultidisciplinary care pathway; and 24 postemergency critical care center, postmultidisciplinary care pathway. A statistically significant reduction in the time from emergency department presentation to initiation of leukapheresis was observed from preemergency critical care center to postemergency critical care center, premultidisciplinary care pathway and postemergency critical care center, postmultidisciplinary care pathway (11.5 vs 7.9 vs 7.7 hr; $p = 0.004$). Statistically significant reductions in in-hospital mortality were observed from preemergency critical care center to postemergency critical care center, premultidisciplinary care pathway and postemergency critical care center, postmultidisciplinary care pathway (64.3% vs 21.9% vs 25.0%; $p = 0.01$). A trend toward decreased inpatient ICU utilization was observed, although was not statistically significant (35.7% vs 12.5% vs 25.0%; $p = 0.14$).

Conclusions and Relevance: Implementation of a multidisciplinary care pathway via use of an emergency department-ICU for critically ill patients with leukostasis was associated with statistically significant reductions in time to leukapheresis and in-hospital mortality. These findings suggest an emergency department-ICU model may allow for maximal resource and care coordination at the point of contact with critically ill patients and improved clinical outcomes.

Key Words: blast crisis; emergency department; emergency department-intensive care unit; leukapheresis; leukemia; leukostasis

Leukostasis is a medical emergency associated with substantial mortality. It develops from white cell plugs in the microvasculature resulting in decreased tissue perfusion and is potentially related to increased blood viscosity from less deformable leukemic blasts obstructing capillary beds (1–4). Leukostasis most commonly occurs in patients with acute myeloid leukemia

or chronic myeloid leukemia in blast crisis, and typical presenting symptoms relate to involvement of the lungs (dyspnea, hypoxia) or CNS (headache, numbness, somnolence, etc.). Additional signs and symptoms can result from decreased tissue perfusion of other organs (myocardial infarction, priapism, limb ischemia, bowel infarction) (1, 4, 5). Mortality associated with leukostasis has been reported as high as 20–40% (6–10). Thus, prompt diagnosis and expedited management are essential.

Management of leukostasis can prove challenging due to the medical complexity, multidisciplinary care coordination, and degree of resources required. Mainstays of initial management include cytoreduction (induction chemotherapy, hydroxyurea, and/or leukapheresis), prevention/management of tumor lysis syndrome, management of coagulation abnormalities including disseminated intravascular coagulation, and supportive care measures including IV hydration. Management requires clinicians from multiple specialties, which at our institution include Emergency Medicine, Hematology, Blood Bank, Clinical Pathology, and Critical Care. This complexity can strain the extent of resources available in the emergency department (ED) setting and potentially lead to delays in care of critically ill leukostasis patients, a diagnosis associated with substantial early mortality.

Prolonged ED boarding of critically ill patients is a challenge facing many healthcare organizations, and ED boarding of greater than or equal to 5 hours has been associated with poor outcomes for critically ill patients (11, 12). Resuscitative care units (including ED-based ICUs) have been implemented in response to this challenge (13), and the ED-ICU model has been associated with reduced risk-adjusted mortality of ED patients and reduced ED to ICU admissions (14). The impact of early, aggressive, coordinated critical care on patients presenting to the ED with leukostasis is unknown.

The objective of this study was to assess the effect of utilization of an ED-ICU and a multidisciplinary care pathway on outcomes of critically ill leukostasis patients presenting to the ED. We hypothesized that implementing a multidisciplinary care pathway through utilization of an ED-ICU would be associated with reductions in time to leukapheresis, rate of ICU admission, and in-hospital mortality.

MATERIALS AND METHODS

Design, Setting, Participants

This retrospective cohort study was conducted at a single large academic medical center in the United States. The Institutional Review Board at the University of Michigan reviewed and approved this study. This study is presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (15).

Adult ED patients with signs and symptoms of leukostasis requiring emergent leukapheresis per hematologist recommendation were included and analyzed via a retrospective review of prospectively collected electronic health records. The premergency critical care center (EC3) cohort included patients presenting from September 2012 to February 2015, and the two post-EC3 cohorts (pre- and postmultidisciplinary care pathway) included patients presenting from February 2015 to May 2019. This date

range (which determined the study size) was selected as a new electronic medical record was deployed at our institution in 2012.

We implemented a hybrid ED-ICU setting (EC3) in February 2015 and subsequently implemented a multidisciplinary care pathway with members from Emergency Medicine, Hematology, Blood Bank, and Clinical Pathology in September 2017 (**Supplemental Fig. 1**, Supplemental Digital Content 1, <http://links.lww.com/CCX/A132>; **legend**, Supplemental Digital Content 2, <http://links.lww.com/CCX/A133>). The interventions in this study (implementation of an ED-ICU and implementation of a multidisciplinary care pathway) may have manipulated processes and/or a patient's environment to modify outcomes.

Main Outcomes and Measures

Age, gender, diagnosis, percent blasts, total ED length of stay (LOS), rate of admission from ED to inpatient ICU, time from ED presentation to initiation of leukapheresis, and in-hospital mortality were collected from the electronic medical record and analyzed. ED LOS in the post-EC3 cohort is inclusive of time in both the main ED and the EC3.

Analysis

Analysis compared three cohorts: 1) pre-EC3; 2) post-EC3, pre-multidisciplinary care pathway; and 3) post-EC3, postmultidisciplinary care pathway. Statistical analysis was performed using SAS software (SAS Institute, Cary, NC). An alpha level of 0.05 was used for all analyses. One-way analyses of variance were used for continuous outcome variables, and chi-squared analyses were performed for categorical outcome variables. Statistically significant effects of cohort were followed-up with post hoc comparisons. Analysis was conducted from July to September of 2019.

RESULTS

A total of 70 patients were identified and included for analysis, 14 pre-EC3 and 56 post-EC3 (**Table 1**). Of the 56 post-EC3 patients, 32 presented to the ED prior to release of our multidisciplinary care pathway, and 24 presented to the ED after release of our multidisciplinary care pathway. Results showed that age was similar across cohorts, $F(2, 57) = 1.2$ ns, and more patients in the two post-EC3 cohorts were male. The three cohorts (pre-EC3; post-EC3, premultidisciplinary care pathway; and post-EC3, postmultidisciplinary care pathway) were not statistically significantly different with respect to diagnosis or percent blasts on presentation.

With implementation of a multidisciplinary care pathway and utilization of an ED-ICU, we observed a statistically significant reduction in the time from ED presentation to initiation of leukapheresis, $F(2, 67) = 6.0$ ($p = 0.004$). Post hoc comparisons showed that time to leukapheresis was longest for pre-EC3 patients ($M = 11.5$ hr) and was statistically significantly shorter for both post-EC3, premultidisciplinary care pathway patients ($M = 7.9$ hr; $p = 0.002$) and post-EC3, postmultidisciplinary care pathway patients ($M = 7.7$ hr; $p = 0.003$). Time to leukapheresis in the latter two cohorts was not statistically significantly different ($p = 0.90$).

With implementation of a multidisciplinary care pathway and utilization of an ED-ICU, a statistically significant reduction in in-hospital mortality was observed, $\chi^2(2) = 8.8$ ($p = 0.01$). Post hoc

TABLE 1. Differences Between Preemergency Critical Care Center; Postemergency Critical Care Center, Premultidisciplinary Care Pathway; and Postemergency Critical Care Center, Postmultidisciplinary Care Pathway Patients

Characteristic	Preemergency Critical Care Center (n = 14)	Postemergency Critical Care Center (n = 56)		P
		Premultidisciplinary Care Pathway (n = 32)	Postmultidisciplinary Care Pathway (n = 24)	
Mean age, yr (sd)	53.9 (±14.1)	52.8 (±19.7)	60.0 (±16.8)	0.31
Male gender, n (%)	6 (42.9) ^a	24 (75.0) ^b	19 (79.2) ^b	0.04
Mean emergency department length of stay, hr (sd)	7.0 ^a (±3.7)	14.1 ^b (±6.6)	18.1 ^c (±5.5)	<0.001
Time to leukapheresis, hr (sd)	11.5 ^a (±5.4)	7.9 ^b (±2.2)	7.7 ^b (±3.8)	0.004
Admission to inpatient ICU, n (%)	5 (35.7)	4 (12.5)	6 (25.0)	0.14
In-hospital mortality, n (%)	9 (64.3) ^a	7 (21.9) ^b	6 (25.0) ^b	0.01
Diagnosis, n (%)				
Acute myeloid leukemia	10 (71)	22 (69)	15 (63)	0.10
Acute lymphoblastic leukemia	1 (7)	3 (9)	4 (17)	0.42
Diffuse large B-cell lymphoma	1 (7)	0	0	0.38
Plasma cell leukemia	1 (7)	0	0	0.38
Mantle cell lymphoma	1 (7)	1 (3)	0	0.61
Other	0	6 (19)	5 (21)	0.06
Percent blasts, mean (sd)	53.7 (37.4)	43.5 (39.5)	67.3 (35.4)	0.07

Analysis compared three cohorts: 1) preemergency critical care center (EC3); 2) post-EC3, premultidisciplinary care pathway; and 3) post-EC3, postmultidisciplinary care pathway. *p* values are from omnibus tests (analysis of variance for continuous variables and χ^2 for categorical variables) and indicate that at least one cohort is statistically significantly different from at least one other cohort. Means and percentages not sharing a common superscript are statistically significantly different from each other at *p* < 0.05 based on post hoc comparisons.

comparisons showed that in-hospital mortality was highest among pre-EC3 patients (64.3%) and was statistically significantly lower for both post-EC3, premultidisciplinary care pathway patients (21.9%; *p* = 0.006) and post-EC3, postmultidisciplinary care pathway patients (25.0%; *p* = 0.02). In-hospital mortality in the latter two cohorts was not statistically significantly different (*p* = 0.84).

While the overall effect of cohort was not statistically significant (*p* = 0.14), inpatient ICU utilization decreased from 35.7% in the pre-EC3 cohort to 12.5% in the post-EC3, premultidisciplinary care cohort, then increased to 25.0% in the post-EC3, postmultidisciplinary care cohort.

DISCUSSION

We observed that implementation of a multidisciplinary care pathway via use of an ED-ICU for ED patients with leukostasis was associated with substantial and statistically significant reductions in time to leukapheresis and in-hospital mortality.

Under recognition, delays in diagnosis, and delays in management can prove lethal for patients with leukostasis, given the extremely high early mortality of this condition. Initial management and resuscitation of patients presenting to the ED with leukostasis is resource intensive, multidisciplinary, and medically complex. Arrangements for cytoreduction (especially via leukapheresis) can be associated with substantial delays if not

undertaken in a coordinated, streamlined fashion, given the multiple required steps and consultants involved.

At our institution, initiating leukapheresis consists of diagnosis/recognition, peripheral smear review, hematology consultation, pathology consultation and coordination for leukapheresis, correction of coagulopathy, placement of a hemodialysis line, and arrangements for an ICU bed. In our Pre-EC3 cohort, the mean time to accomplish these tasks was 11.5 hours, with a maximum of 25.2 hours. Furthermore, coordination among subspecialists (which at our institution include Hematology, Blood Bank, Interventional Radiology, and Clinical Pathology) can prove extremely challenging in a busy ED setting, especially as many U.S. EDs are facing increasing volume and acuity of critically ill patients (16). Our results showed an average reduction of more than 3 hours in time to leukapheresis in both post-EC3 cohorts, and this may have contributed to the substantial reductions in mortality observed in both Post-EC3 cohorts.

An ED-based ICU is one strategy to address the increasing critical care requirements despite decreasing ICU availability facing many EDs across the United States. This unique setting provides one solution to the “Right Care, Right Now” approach championed by the Society of Critical Care Medicine (17). One of the founders of critical care, Ake Grenvik, predicted decades ago that “Many critically ill patients

no longer need admission to the hospital if the diagnostic work-up and treatment may be completed in an ED short-term ICU” (18).

These findings suggest an ED-ICU model, through use of a multidisciplinary care pathway, may allow for maximal resources and care coordination at the point of contact with critically ill patients. Future research is needed to quantify the impact of an ED-ICU on additional critically ill patient populations and disease states, including at other institutions, to assess external validity and generalizability.

LIMITATIONS

Several limitations of this study are appreciated. The observational nature of this study limits interpretation of results to association, and we are unable to draw causal inferences. This study was conducted at a single academic medical center in the United States, and generalizability of results is uncertain. The sample size in each cohort is relatively small, given the relative infrequency of ED presentation of the diagnosis of leukostasis. The before-and-after nature of this study is inherently prone to favoring of the “after” cohort. The pragmatic, uncontrolled nature of this study may contribute to the differences observed. The quality improvement efforts assessed in this study were implemented in 2015. Since 2015, some studies have suggested no benefit of leukapheresis for patients with leukostasis (19–21). The intention of this study was not to report on the efficacy of leukapheresis but rather was to report on the effect of an ED-ICU and a multidisciplinary care pathway on outcomes of critically ill leukostasis patients presenting to the ED.

CONCLUSIONS

Implementation of a multidisciplinary care pathway via use of an ED-ICU for critically ill ED patients with leukostasis was associated with statistically significant and clinically meaningful reductions in time to leukapheresis and in-hospital mortality. These findings suggest that an ED-ICU model may allow for maximal resource and care coordination at the point of contact with critically ill patients. Future research is needed to quantify the impact of an ED-ICU on additional critically ill patient populations and disease states.

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