Clinical outcomes and transfusion management following intracranial hemorrhage in patients with acute leukemia

Shannon Nixon,[1,2] Lani Lieberman,[1,2] Eshetu G. Atenafu,[1,2] Mary Doherty,[1,2] Cindy Murray,[1,2] Amanda Wolfe,[1,2] Danielle Brandys,[1,2] Suzanne Rowland,[1,2] Benjamin YM Kwan,[1,2] Eugene Yu,[1,2] Breanne Lechner,[1,2] and Dawn Maze[1,2]

BACKGROUND: There is little evidence to guide management of patients with acute leukemia and intracranial hemorrhage (ICH). Predictors of long-term outcome following ICH are unknown.

STUDY DESIGN AND METHODS: This study included adult patients with acute leukemia and ICH over an 8-year period. The primary outcome was data regarding 90-day mortality. Secondary outcomes included data related to the proportion of patients receiving post-remission therapy and predictors of 90-day mortality.

RESULTS: ICH occurred in 101 patients; 12 patients died within 72 hours. For the 89 others, 90-day mortality was 40%. Of 43 patients who received induction, 30 achieved remission and 26 received post-remission therapy. Older age (p = 0.03) and higher white count (p = 0.02) at the time of ICH were predictive of inferior survival. During 90-day follow-up, median platelet count was 37 x 10^9/L (0-1526 x 10^9/L). Lower platelet count during follow-up was predictive of 90-day mortality (p = <0.01). Twenty-one percent of platelet transfusions were provided when the platelet count was less than 10 x 10^9/L, 54% between 10 and 29 x 10^9/L, and 25% greater than 30 x 10^9/L. New or progressive ICH occurred in 23 patients. There was no difference in the median platelet transfusion trigger between patients who had new or progressive ICH and those who did not.

CONCLUSION: In patients with acute leukemia, survival following ICH is poor. Older age and higher white count is associated with increased mortality, perhaps reflecting higher risk disease. Following ICH in acute leukemia platelet transfusions do not appear to alter the risk of progressive bleeding or mortality.

Intracranial hemorrhage (ICH) is a rare but serious complication in adult patients with acute leukemia with an estimated incidence of 3-6%[1–3] and a mortality rate of up to 67% within 30 days.[2] Those patients who survive ICH can be faced with significant morbidity. Multiple factors may contribute to the increased bleeding risk in acute leukemia including coagulopathy, leukemic infiltration, and thrombocytopenia.

The relationship between thrombocytopenia and hemorrhage was first reported in 1962 when Gaydos et al. observed an inverse relationship between the platelet count and the number of days of bleeding in patients receiving treatment for acute leukemia.[4] Subsequent studies supported the use of prophylactic platelet transfusions in this patient population to reduce the risk of bleeding,[5–7] with current guidelines recommending platelet transfusion when the platelet count is less than 10 x 10^9/L to reduce the risk of spontaneous hemorrhage.[8,9] Higher thresholds are often recommended in situations where there may be an increased risk of bleeding, such as a requirement for therapeutic anticoagulation or prior to invasive procedures, however there is little evidence available to support a specific platelet transfusion threshold, particularly in patients who have had serious bleeding events.

Following ICH, clinical judgment would support improving thrombocytopenia to reduce the risk for new or progressive bleeding, and potentially, mortality. However, in the absence of evidence, there is uncertainty with respect to

From the [1]Princess Margaret Cancer Centre, University Health Network, and the [2]Department of Medicine, University of Toronto, Toronto, Canada.

Address reprint requests to: Dawn Maze, MD, FRCPC, MSc, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, 610 University Avenue, OPG building 6th floor, 6-324, Toronto ON M5G 2M9; e-mail: dawn.maze@uhn.ca.

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the target platelet count and the duration that it should be maintained. One retrospective review evaluated 76 patients diagnosed with acute leukemia who experienced ICH and found that reaching and maintaining a platelet count >50 x 10^9/L did not correlate with improved 30-day mortality.[10] For those who survived the initial 72 hours following ICH, the 30-day mortality of 32.7% was largely attributed to non-ICH causes. Other studies have shown 30-day mortality to be associated with factors other than thrombocytopenia, including patient age, location of ICH, prolongation of PT, and sepsis.[1,2]

Uncertainty remains regarding the predictors for poor clinical outcomes following ICH. Prevention of new or progressive bleeding remains a clinical concern, and optimal platelet transfusion management is unclear. The objectives of this study were to assess incidence and type of ICH, clinical characteristics of acute leukemia patients who experience ICH, and to identify predictors of 90-day mortality.

STUDY DESIGN AND METHODS

Patient characteristics

This research ethics board-approved retrospective study included all adult patients with a diagnosis of acute leukemia and ICH at the Princess Margaret Cancer Centre in Toronto, Canada between January 1, 2009 and December 31, 2016. Patients greater than 18 years of age with a diagnosis of acute leukemia and a documented ICH during the study period were included. Patients with acute leukemia were identified through the local cancer centre registry.

Baseline characteristics were collected including age, sex, diagnosis, European Leukemia Net (ELN) risk category,[11] and relevant comorbidities (such as hypertension and diabetes). Additionally, clinical data on the day of ICH and 7 days prior was collected including type of leukemia, disease status, treatment details, central nervous system (CNS) status, relevant laboratory data, medications known to increase risk of bleeding, use of tranexamic acid, clinical signs of bleeding at other sites (hematuria, hematemesis, petechial) and evidence of sepsis. Sepsis was defined as any positive blood culture combined with a positive systemic inflammatory response syndrome (SIRS) score.[12] A positive SIRS score was achieved if 2 or more criteria were met; heart rate > 90 beats/min, respiratory rate > 20 breaths/min, and temperature > 38 or < 36°C. Leukocytosis and leukopenia were excluded from the original definition of SIRS as these variables may not be as reflective of sepsis in this population.

Intracranial hemorrhage

Patients with ICH were identified with ICD10 codes (ICD 10-160-162, 167). The ICH was categorized as spontaneous or precipitated by a traumatic event within 24 hours. In cases of spontaneous ICH, the indications for brain imaging were captured. All brain computed tomography (CT) or magnetic resonance imaging (MRI) scans were reviewed by neuroradiology to determine the location(s) of ICH.

Thrombocytopenia and platelet transfusions

First morning platelet counts were collected on the day of ICH, 7 days prior to ICH, and during 90-days of follow-up. First morning platelet count refers to the actual platelet count on the day of, and prior to, any platelet transfusion if given. The median platelet count in the week preceding ICH was determined by calculating the median of the first morning platelet counts in the 7 days prior to ICH. Similarly, the median 90-day platelet count was determined by calculating the median of the first morning platelet counts in the 90-days following ICH.

History of transfused random donor or HLA-matched platelets was collected on the day of ICH, 7 days prior to ICH, and during 90-days of follow-up. Platelet transfusion triggers were determined based on the actual platelet count immediately prior to transfusion to reflect clinical practice. For those patients who had a platelet count performed within 1 hour of platelet transfusion, platelet refractoriness was assessed. Platelet transfusion refractoriness was defined as failure to increase the post-transfusion platelet count by 10 x 10^9/L within 1 hour of platelet transfusion. History of transfused fresh frozen plasma and cryoprecipitate was collected on the day of ICH and 7 days prior to ICH.

Clinical outcomes

The primary outcome was 90-day mortality data for those patients who survived the initial 72 hrs following ICH. Secondary outcomes included data regarding 30- and 90-day mortality, proportion of patients who went on to receive post-remission therapy, predictors of 90-day mortality, and overall survival. Factors included in the univariate analysis were age, ELN risk category,[11] location of ICH, leukocyte on day of ICH, platelet count on day of ICH, evidence of platelet refractoriness, median 90-day platelet count following ICH, and presence of new or progressive ICH. Factors included in the multivariable analysis were age, leukocyte on day of ICH, and median 90-day platelet count following ICH. Cause of death and neurologic sequelae were recorded. Minor neurologic sequelae was defined as the presence of mild dysarthria or mild hemiparesis. Major neurologic sequelae was defined as the presence of aphasia, severe hemiparesis, severe cognitive impairment, or severe functional impairment.

All brain CT or MRI scans were reviewed by neuroradiology to determine the presence of initial ICH and any new or progressive bleeding. In cases with reported new or progressive ICH, brain imaging was independently reviewed by a second neuroradiologist who was blind to the initial report to determine if the ICH was stable with expected evolution or edema, or if new or progressive bleeding had occurred. Expected evolution of the hemorrhages included decreased size, decreased mass effect, and appropriate temporal changes in density. New

or progressive bleeding was determined based on increased size, changes in density and new foci of bleeding.

Statistical analyses

Descriptive statistics were used to describe selected baseline characteristics. Categorical variables such as risk stratification and location of ICH were summarized with counts and percentages. Continuous variables such as age at initial ICH, baseline platelet and leukocyte counts, and follow-up were summarized with means, standard deviation, medians and/or ranges as appropriate. Timing of bleed from start of induction was compared for different leukemia diagnoses using Kruskal-Wallis test. Time-to-event was calculated in months from the date of initial ICH to the date of death or last follow-up, whichever comes first for OS. OS rates were calculated using the Kaplan–Meier product-limit method.

For patients surviving beyond 72 hours post ICH, log-rank test was used as a univariate analysis to assess the relationship of 90-day mortality with potential predictive factors. A logistic regression model was used for modeling the 90-day mortality to assess the relationship of potential covariates of interest as a univariate analysis. A multivariable logistic regression model for 90-day mortality was performed for assessing the joint effect of factors based on the univariate result as well as clinical importance. Results were considered to be significant if $p < 0.05$. Statistical analyses were performed using version 9.4 of the SAS system for Windows (2002-2012 SAS Institute, Inc.).

RESULTS

Patient characteristics

During the study period, 2578 patients were diagnosed with acute leukemia and 101 (3.9%) experienced an ICH. The incidence was 4.4% (85/1943) in patients with AML, 1.4% (6/436) in patients with ALL and 6.3% (9/143) in those with APL. Additional patient demographics and clinical characteristics are highlighted in Table 1. At the time of ICH 61 patients were newly diagnosed; 24 (39%) had not yet received any therapy and 28 (46%) were undergoing induction when the bleed occurred. The remainder of newly diagnosed patients were receiving low dose chemotherapy or best supportive care. Seven patients were in complete remission at the time of ICH. Thirty-three patients had relapsed or refractory disease at the time of ICH, 5 of whom had received prior allogeneic transplant. Of the relapsed or refractory patients, 2 (6%) had not yet received any therapy and 5 (15%) were undergoing reinduction when the bleed occurred. The remainder were receiving low dose chemotherapy or best supportive care. For patients receiving induction, the median time from the start of therapy to ICH was 14 days (range 2-56 days) for patients with AML, 14 (9-19) days for patients with APL and 8 (8-30) days for those with ALL ($p = 0.9$).

TABLE 1. Clinical characteristics of ICH among patients with acute leukemia

Characteristic	n = 101
Age, median (range)	63 (21-88)
Female sex, n	58
Hypertension, n	42
Dyslipidemia, n	33
Diabetes, n	16
Leukemia diagnosis, n	
AML	85
APL	9
B-ALL	5
T-ALL	1
MPAL	1
ELN Risk Stratification for patients with AML, n	
Favorable risk	5
Intermediate risk	45
Adverse risk	22
Unknown	18
CNS disease, n	10
WBC x 10^9/L on day of ICH, median (range)	1.80 (0.0-368.0)
Number of patients with WBC > 50, n	5
Number of patients with WBC > 100, n	5
Hb (g/L) on day of ICH	83 (51-129)
Coagulation tests on the day of ICH	
INR	1.28 (0.95-3.43)
aPTT	31 (22-131)
Fibrinogen	3.26 (0.43-8.8)
Sepsis in 7 days prior to ICH, n	5
Positive blood cultures in 7 days prior to ICH, n	9
Clinical evidence of bleeding in 7 days prior to ICH, n	64
Tranexamic acid use in 7 days prior to ICH, n	62
Antiplatelet or anticoagulant in 7 days prior to ICH, n	5
Acetylsalicylic acid	1
Tinzaparin	3
Warfarin	1

Sepsis as defined by modified SIRS criteria.
AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia/lymphoma; APL = acute promyelocytic leukemia; MPAL = mixed phenotype acute leukemia; ELN = European leukemia Net; CNS = central nervous system; WBC = white blood count; Hb = hemoglobin; ICH = intracranial hemorrhage.

Intracranial hemorrhage

In 20 cases, ICH was diagnosed following a fall. Of the 81 patients with spontaneous ICH, the indications for brain imaging were headache in 31, confusion or altered level of consciousness in 29, abnormal neurologic examination in 10, visual or auditory changes in 6, seizures in 2, and vomiting in 1. In the 2 remaining cases, ICH was discovered incidentally on CT head scans performed for unrelated reasons. Fifty-five patients had subdural hemorrhage, 25 had intracerebral hemorrhage, 6 had subarachnoid hemorrhage, 1 had epidural hemorrhage, and 13 patients experienced hemorrhage in multiple locations of the brain.

TABLE 2. Proportion of actual platelet transfusion triggers in the 90 days following ICH

Platelet count prior to transfusion (x 10^9/L)	Percent (%)
<10	21
10 or more but <20	30
20 or more but <30	25
30 or more but <50	17
≥50	8

Thrombocytopenia and platelet transfusions

Within 7 days of ICH, the median morning platelet count was 17 x10^9/L (range 0-433 x10^9/L). Fourteen patients exhibited evidence of platelet transfusion refractoriness and 9 were receiving HLA-matched platelet products. Eleven patients had received fresh frozen plasma and/or cryoprecipitate within 7 days of ICH.

On the day of ICH, the median morning platelet count was 16 x 10^9/L (range 0-433 x 10^9/L). Thirty-one patients had a platelet count of less than 10 x 10^9/L and 10 of these patients had received a platelet transfusion prior to ICH diagnosis. Seventy patients had a platelet count ≥10 x 10^9/L and 17 of these patients had received a platelet transfusion prior to the bleed. Three patients received fresh frozen plasma and two patients received cryoprecipitate prior to ICH.

Those patients who survived the initial 72 hours following ICH were included in the 90-day thrombocytopenia and platelet transfusion analysis. During the 90-day period, the median morning platelet count was 37 x 10^9/L (range 0-1526 x 10^9/L). Twenty-one percent of platelet transfusions were provided for a morning platelet count of less than 10 x 10^9/L, 54% for a platelet count between 10 and 29 x 10^9/L, and 25% for a platelet count greater than 30 x 10^9/L (Table 2).

Clinical outcomes

The median OS of the entire cohort (n = 101) was 4.3 (95% CI 1.2-6.8) months (Fig. 1). Causes of death were disease in 48 patients, ICH in 17, infection in 8, treatment-related mortality in 6, and unknown in 1. Twelve patients died within 72 hours following ICH.

For those patients who survived the initial 72 hours (n = 89), 30- and 90-day mortality rates were 24% and 40%, respectively. Of 43 patients who received induction, 30 achieved complete remission and 26 went on to receive post-remissive therapy. Twenty-three patients experienced a new or progressive ICH with median time to progression of 9 days (range 0-35), 5 had minor neurologic sequelae, and 15 had major neurologic sequelae. Potential predictors of 90-day mortality are shown in Table 3. Older age (p = 0.03) was predictive of poorer 90-day survival on multivariate analysis. Higher white blood cell count (p = 0.02) at the time of ICH was predictive of poorer 90-day survival on univariate analysis, but not on multivariate analysis. Neither ELN risk category (p = 0.69), site of bleeding (p = 0.21), platelet count at the time of the bleed (p = 0.45), nor the presence of platelet refractoriness (p = 0.68) were associated with inferior survival.

The median morning platelet count over the 90-day period was predictive of 90-day mortality on multivariate analysis ($p \leq \underline{0.01}$). The median morning platelet count over the 90-day period was 36 x 10^9/L (range 0-213 x 10^9/L) in those who had further bleeding and 37 x 10^9/L (range 0-1526 x 10^9/L)

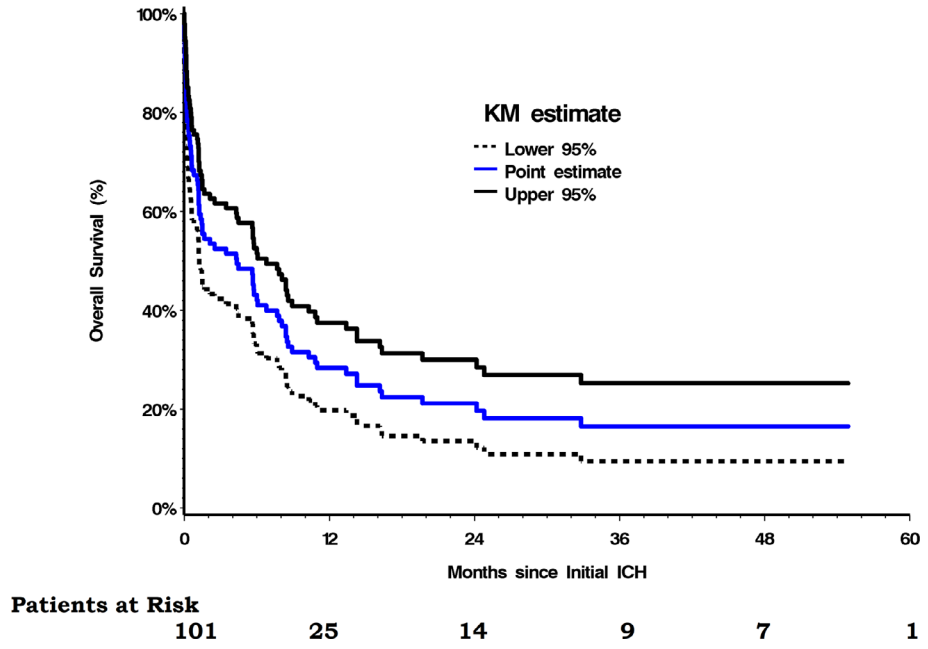

Fig. 1. Overall survival distribution. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3. Univariate and multivariate analysis of predictors of 90-day mortality

	Univariable	Multivariable	
Risk factor	p-value	p-value	HR (95% CI)
Age	0.02*	0.03	1.05 (1.01-1.10)
ELN risk stratification	0.69		
Location of ICH	0.21		
Leukocyte on day of ICH	0.02*	0.22	1.02 (0.99-1.05)
Platelet count on day of ICH	0.45		
Median 90d platelet count	<0.01*	<0.01	0.97 (0.94-0.99)
Platelet refractoriness	0.68		
New or Progressive ICH	1.00		

* Indicates statistical significance

in those who did not (p = 0.09). The median morning platelet count prior to platelet transfusion was 21 x 10^9/L (0-93 x 10^9/L) in those with subsequent bleeding versus 19 x 10^9/L (0-114 x 10^9/L) in those without (p = 0.13). Neither the median morning platelet count nor the median morning platelet transfusion trigger differed between those patients who had new or progressive ICH and those who did not.

DISCUSSION

The incidence of ICH for acute leukemia patients in this study was 4%, similar to rates reported by others.[2,3,13] Early death was common (12%) and among those who survived the initial 72 hours following ICH, outcomes remained poor. Understanding risk factors for long term mortality in patients with acute leukemia and ICH is of clinical importance.

In our patient population, older age and higher leukocyte count on the day of ICH were found to be significant predictors of 90-day mortality on univariate analysis, and may be indicative of a more serious bleed. The literature reports the following risk factors for mortality following an ICH: location of the bleed,[2] prolonged PT,[2,3] leukocytosis,[3,14] older age[10,13] and relapsed disease status.[13] To date, only one study identified thrombocytopenia, specifically platelet count under 35 x 10^9/L as a risk factor for mortality.[3] In our study, platelet count on the day of ICH was not a significant risk factor for 90-day mortality, however the median 90-day platelet count following ICH was found to be predictive. The majority of our patients had an ICH at initial diagnosis and prior to achieving complete remission following induction chemotherapy. It is hypothesized that those who were able to complete induction chemotherapy and recover sustained platelet counts, had improved outcomes, while those who experienced detrimental treatment delays impacting count recovery, did poorly. This is supported by the fact that the cause of death was the primary disease in half of the patients in this cohort.

There is high quality evidence to support prophylactic platelet transfusions to reduce the risk of hemorrhage in patients with acute leukemia. Following ICH, clinical judgment would support improving thrombocytopenia by using higher platelet transfusion thresholds than the recommended trigger of 10 x 10^9/L[15,16] to prevent new or progressive bleeding. At the MD Anderson Cancer Centre, platelets are transfused to a target platelet count of 50 x 10^9/L following ICH in acute leukemia.[10] In a retrospective study evaluating the feasibility of this approach, only 32% of patients achieved the target and the actual median platelet count that was achieved was 16.5 x 10^9/L. While platelet refractoriness was a risk factor for mortality, neither achieving nor maintaining the platelet count target of 50 x 10^9/L was beneficial for survival. In our study, platelet transfusion practice was highly variable following the initial ICH event. Guidelines regarding platelet transfusion thresholds following an ICH event are not available in our institution or in the literature leading to this variable practice.

ICH in acute leukemia results in very poor outcomes. In our study, the median overall survival was less than 5 months. In a recent population-based study, the median survival of patients with AML treated at academic institutions was 12.6 months.[17] The most common cause of death in our patient population was progressive disease while few died due to ICH. New or progressive bleeding occurred in 26% and was not impacted by platelet transfusion practice, suggesting that the primary focus should be on prevention of the initial bleed. One fifth of the bleeding events in this study were traumatic suggesting that strategies to reduce falls may reduce the incidence of ICH. The InCite study is a UK-wide nested case–control within a 4-year prospective surveillance that will hopefully provide a more precise estimate of incidence and identify risk factors for the initial ICH.[18] This study, which has been published in abstract form, identified 148 ICH cases over the 4-year study period;[8] 30-day mortality was 50% and risk factors for bleeding were leukocytosis, platelet refractoriness, elevated CRP, and female sex.

The present study has several limitations. Because the review was performed at a large quaternary cancer centre with multiple community outreach partners, the ICH incidence is likely underestimated. Small sample size limited the ability to accurately determine the associations between outcomes and predictive variables with low event rates, such as sepsis. Additionally, our revised SIRS definition of sepsis to exclude leukocytosis and leukopenia was not validated in our patient population. Similar to other retrospective analyses, the present study is prone to recall bias (e.g., comorbidities may not be complete) such that an unidentified risk factor may be related to risk of ICH recurrence. Other risk factors as described above and biomarkers of ICH in the general populations, such as D-dimer,[19] soluble CD163,[20] or troponin[21] were not collected. Whether these risk factors are also risk factors in the leukemia population is presently unknown. A case control study or prospective cohort study would allow the collection and analyses of these risk factors.

In summary, in patients with acute leukemia, survival following ICH is poor. Older age and higher white cell count may be associated with increased mortality. Improving thrombocytopenia is of unclear clinical benefit in reducing the risks of progressive bleeding and mortality. Platelet transfusions do not

appear to alter the risk of progressive bleeding, and factors other than platelet transfusion practice likely contribute to the overall poor prognosis. Until further prospective data are available, fall prevention, aggressive correction of coagulopathy, cytoreduction and management of sepsis may reduce the risk of developing ICH.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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