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Incidence and Predictors of Respiratory Adverse Events during Induction Therapy in Children with Acute Myeloid Leukemia

by

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Incidence and Predictors of Respiratory Adverse Events during Induction Therapy in Children with Acute Myeloid Leukemia

by

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M.D., Medical College of Georgia, 2012

Advisor: William G. Woods, M.D.

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Abstract

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by Lane H. Miller

Background: Survival in childhood acute myeloid leukemia (AML) has plateaued at 60-70%, with induction death occurring in 4-11% of patients. While pulmonary complications are known to contribute to pediatric AML induction morbidity and mortality, our understanding of the incidence, categories, and risk factors for respiratory adverse events (AEs) is incomplete.

Objectives: To estimate the incidence of respiratory AEs occurring during induction therapy for pediatric AML, categorize and grade these AEs, and identify risk factors for AE development.

Methods: Using manual chart abstraction, we retrospectively followed a cohort of *de novo* pediatric AML patients (age ≤ 21) from initial presentation through day 42 of induction chemotherapy. Outcomes included any NCI CTCAE grade 2-5 respiratory AE or death from another cause. Demographic, disease, and treatment-related data were abstracted. Descriptive statistics, survival analysis, bivariate analysis, and multivariable analysis were performed (SAS v9.4, Cary, NC).

Results: Among 113 eligible subjects, 53.1% (n = 60) experienced 74 grade 2-5 respiratory AEs. Mechanical ventilation was required in 23% of all respiratory AEs (n = 17). Peaks in incidence occurred between days 0-7 and days 14-21. Induction death occurred in 4.4% (n = 5). Fluid overload at any time (aOR 47.6 [95% CI: 5.7-395.1]) and older age at diagnosis (aOR 1.12 [95% CI: 1.01-1.24]) were estimated to be associated with AE occurrence. Positive fluid overload status (aHR 5.63 [95% CI: 3.42-9.29]), positive infection status (aHR 2.29 [95% CI: 1.30-4.02]), elevated initial WBC (aHR 1.003 [95% CI: 1.000-1.005]), and male gender (aHR 1.59 [95% CI: 1.05-2.38]) were estimated to be associated with increased hazard for AE development.

Conclusion: We describe a higher incidence of respiratory AEs during childhood AML induction than previously described. Fluid overload at any time and older age at diagnosis are associated with AE development. Positive fluid overload status, positive infection status, elevated initial WBC, and male gender were associated with increased hazard for AE development. Interventions focused on fluid overload and infection prevention and management should be further addressed in this population to reduce early respiratory complications and prevent potential morbidity and mortality.

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A. INTRODUCTION

Acute myeloid leukemia (AML) is the second most common form of childhood leukemia with overall survival remaining stagnant at 60-70% over recent decades (1-6). Pediatric *de novo* AML patients are at a particularly increased risk of death during induction, the first phase of chemotherapy, which is reported in 4-11% of all patients (5, 7-13). Induction mortality is well described in the literature, with several demographic and disease-related risk factors having been previously identified (5-7, 14-16). While pulmonary complications have been intermittently reported among pediatric AML induction mortality and morbidity statistics, our overall understanding of the incidence, categories, severities, patterns, and risk factors for respiratory adverse events (AE) remains incomplete.

Respiratory AEs during AML induction can develop in the context of a number of pathophysiologic processes, including leukemia-specific lung involvement (pulmonary leukostasis, pulmonary leukemic infiltration (PLI), acute lysis pneumopathy (ALP)), pulmonary infection, chemotherapy-induced pulmonary toxicity, and iatrogenic pulmonary edema (17-29). However vital sign changes, physical exam findings, and chest imaging are oftentimes nonspecific in these particular etiologies, making diagnosis and directed management difficult. Measures of preventing these pathophysiologic processes (e.g. leukapheresis, prophylactic antimicrobials, net-neutral fluid balance) are also either poorly understood, ineffective, or inconsistently applied from one institution to the next (15, 30-41).

The goals of this single institution, retrospective cohort study are to estimate the incidence of respiratory AEs that occur during induction therapy in *de novo* pediatric AML, to categorize and grade these AEs, to describe the temporal course of respiratory

AE development, and to identify potentially modifiable predictors of respiratory AE development.

B. BACKGROUND

Survival in pediatric acute myeloid leukemia

Acute myeloid leukemia (AML) is the second most common form of childhood leukemia, with roughly 650 cases diagnosed annually in the United States in children under the age of 20 (1, 42). While data from the recently closed Children's Oncology Group (COG) AAML1031 phase 3 trial for *de novo* AML have not yet been made public, as of most recent evaluation, pediatric AML patients experience 90% remission induction and 65-70% overall survival (OS) (2-6). Two specific subsets of AML patients, those with acute promyelocytic leukemia (APL) and those with Down syndrome, consistently fare better in terms of event-free survival (EFS) and OS. Since the addition of all-trans retinoic acid (ATRA) as the backbone of therapy, APL OS has dramatically improved and was noted to be 94% on the most recent COG trial (43). Down syndrome AML requires substantially less chemotherapy to achieve remission and cure, and as such, OS was noted to be 93% on the most recent COG trial (44). All told, much of the considerable improvement in pediatric AML survival over recent decades is attributable to enhancements in supportive care, particularly prevention and treatment of systemic bacterial and fungal infections. Within the Children's Cancer Group (CCG) 2961 phase III pediatric *de novo* AML trial, survival significantly improved between the earlier years of the study (OS 44% between 1996-1998) and the latter portion (OS 58% between 2000-2002). This was a remarkable development related to significantly decreased treatment-related mortality (TRM) in the context of newly instituted standardized supportive care guidelines only consistently applicable to those in the later cohort (mandatory hospitalization during periods of neutropenia, empiric broad spectrum antibiotics with

fever, preemptive fungal coverage with prolonged fever, fungal surveillance with CT imaging, and reduced steroid use) (45).

Induction morbidity and mortality in pediatric acute myeloid leukemia

At the time of diagnosis, AML patients can present with respiratory distress, hemodynamic instability, coagulopathy, neurologic abnormalities, renal injury, and infection (7, 8, 14). With the initial phase of medical management, involving high dose chemotherapy and a prolonged myelosuppressed period, patients become further predisposed to critical illness. Among all pediatric acute leukemia patients of the POGONIS system between 1990-2010, AML diagnosis was independently associated with early death (7). Similarly, in a review of all children aged < 20 between 1992-2011 from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) 13 registries, AML demonstrated the highest odds ratio of death within 1 month of diagnosis among all pediatric hematologic malignancies and the second highest odds ratio of death during that same time frame among all pediatric cancers (9). In adult AML patients, risk of death collectively decreases after 4 weeks from chemotherapy initiation, regardless of age, although similar data is not established in children (10).

Day 42 is a commonly assigned cutoff date for induction mortality, as by this point in therapy, marrow recovery (as defined by attainment of an absolute neutrophil count > 750 cells/mm^3 and platelet count > 75,000 platelets/mm^3) has typically been attained (7, 11). Numerous studies have looked at the incidence, etiologies, and risk factors of induction mortality in pediatric AML, noting anywhere from 4-11% incidence in the period from initial presentation until 42 days after the start of treatment (5, 7-13). Induction death in both AML and acute lymphoblastic leukemia

(ALL) patients is typically treatment-related (7). In a recent analysis of the St Jude institutional experience, early death (death prior to completion of the induction I chemotherapy cycle) and death while in first complete remission (CR1) decreased from 18.5% during the 1997-2003 period to 7.9% during the 2002-2008 period (5), demonstrating a progressive improvement in the incidence of treatment-related early mortality over time. In a recent review of pediatric *de novo* AML patients in the PHIS database from 2004-2014, 50% of induction I deaths occurred within 10 days of hospital admission (46).

The causes of induction death have been shown to differ between the time of presentation until day 14 of chemotherapy administration when compared with those that occur between days 15 and 42. Bleeding and complications of leukostasis underlie central nervous system, pulmonary, and gastrointestinal events during this early phase. Infection, on the other hand, results in a larger proportion of mortality observed in the later phase (11).

Previously identified risk factors for induction death in AML have included age < 2 years or ≥ 10 years at diagnosis, hyperleukocytosis at initial presentation (WBC ≥ 100 x 10^3 cells/μL), FAB M4 and M5 morphology, central nervous system (CNS) disease at diagnosis, female gender, Black race, Hispanic ethnicity, low or elevated body mass index (BMI), receipt of public insurance, and poor performance status at the time of initial presentation (5, 6, 11, 14-16). More specifically, within the AML-BFM 93 and 98 trials, hyperleukocytosis, poor performance status, and FAB M5 morphology were found to be risk factors for death ≤ 14 days using multivariable logistic regression analysis (11).

Respiratory complications in pediatric acute myeloid leukemia

Respiratory adverse events (AEs) certainly contribute to AML morbidity and mortality during induction, however our overall understanding of the incidence, severity, patterns, and risk factors for these events remains incomplete. Proposed risk factors to date for respiratory AEs during induction include hyperleukocytosis, FAB M4 or M5 morphologic subtype, and poor performance status at the time of diagnosis (17).

In the early phase of induction therapy, leukemia-specific lung involvement through pulmonary leukostasis, pulmonary leukemic infiltration (PLI), and acute lysis pneumopathy (ALP) are well-described phenomena (17-20). AML blasts tend to be larger than typical leukocytes, as evidenced by higher forward scatter on flow cytometric analysis, with particularly adherent properties and decreased deformability, all potentially predisposing to leukemia-specific lung involvement through infiltration of the pulmonary small vasculature and interstitium (21, 22, 47). In a single institution cohort analysis at the Hospital for Sick Children in Toronto between 1992 and 2005, 12.5% of pediatric AML patients presented with hyperleukocytosis. Among those patients, a WBC > 200 x 10^3 cells/µL was associated with severe pulmonary leukostasis requiring mechanical ventilation (18). On the COG AAML03P1 and AAML0531 phase III trials (2003-2010), 18.8% of *de novo* AML patients presented with hyperleukocytosis, a group which experienced a significantly higher incidence of Grade 3-5 hypoxia (30.5%, $p < .001$) and Grade 3-5 pulmonary hemorrhage (3.1%, $p < .001$) (4). On the St Jude AML 91 and 97 protocols (1991-2002), 3.2% of *de novo* AML patients experienced grade 3-4 pulmonary complications during the first 7 days of treatment, all of whom were retrospectively diagnosed with ALP as defined by meeting criteria for tumor lysis

syndrome (TLS) as well as systemic inflammatory release syndrome (SIRS) at the time of the respiratory AE (20).

Pulmonary infection, whether bacterial, viral, or fungal in origin, can certainly promote the development of respiratory AEs. On the BFM-2004 clinical trial for *de novo* pediatric AML (2004-2010), 148 episodes of clinically and/or microbiologically documented infection occurred among 405 patients during their induction course. Pulmonary infections accounted for 36.5% of these episodes (n = 54), which was the second most common infection site excluding blood (23). On the CCG 2891 trial, 4% of patients experienced life-threatening or fatal pulmonary or upper respiratory infections during AML induction, largely accredited to fungal infection (77.4% of all life-threatening or fatal pulmonary infections and 30.4% of all life-threatening or fatal upper respiratory infections) (24). Life-threatening infections prior to the initiation of induction chemotherapy in pediatric AML are extremely rare occurrences. In a review of 328 children treated at 15 Canadian sites between 1995-2004, only 4 cases of bacteremia and 1 case of invasive fungal infection were noted between initial presentation and start of chemotherapy, with 0% infection-related mortality during that time period (25). Evidence does however suggest an underreporting of infectious complications (26, 48) and a potential under diagnosis of invasive fungal infection (49) in this patient population.

Pulmonary edema can also contribute to respiratory complications, either as a result of an underlying cardiogenic pathology, cytarabine toxicity, bortezomib toxicity, or iatrogenic fluid overload. Anthracycline-induced cardiac failure and resultant cardiogenic pulmonary edema is certainly a concern in this population given the standard use of anthracyclines throughout AML treatment. However, a review of the MRC-AML 10 phase III clinical trial for *de* novo pediatric AML (1988-1995) showed

no instances of cardiac failure-related mortality during this 1st and 2nd courses of chemotherapy, suggesting that anthracycline-induced cardiotoxicity manifests itself later in treatment (8). Cytarabine is the principal chemotherapy agent used in AML induction and has been associated with non-cardiogenic pulmonary edema, although this is more frequently reported in adults (27). Bortezomib, a chemotherapy agent emphasized in the most recent COG AAML1031 trial, has also been rarely linked to pulmonary edema and various additional pulmonary toxicities (28). Finally, iatrogenic fluid overload should also be considered in this patient population. To date, the predominance of fluid overload literature in the pediatric population has related to sepsis syndromes (29) and acute renal failure (30), with fluid overload consistently being associated with worse outcomes. For instance, in a single center, retrospective evaluation of pediatric ICU patients, peak fluid overload percentage (calculated daily as net fluid balance from the time of ICU admission divided by ICU admission weight in kilograms multiplied by 100%) predicted a worse oxygenation index and was associated with increased hospital and ICU lengths of stay, controlling for age, gender, and severity of illness (29). At the time of initial presentation, newly diagnosed pediatric AML patients are provided hyper hydration consisting of copious volumes of fluid infused in an effort to prevent renal injury and leukostasis complications, typically at a rate of 125 ml/m^2/hour or 2-times the maintenance fluid rate (50). This is a practice commonly maintained at our institution regardless of age, gender, initial WBC, blast type, or kidney function. Fluid overload is not included in the NCI CTCAE v4.0 list of adverse events used in this study nor the NCI CTCAE v5.0 recently introduced in late 2017 and, as such, the incidence of fluid overload is not reported on most pediatric oncology therapeutic protocols. Fluid overload is also not consistently defined in the pediatric literature, with definitions typically relating to percent weight change from baseline, daily fluid balance, and

physical exam findings (29, 51, 52). Lung ultrasound has been shown to be a highly sensitive method of detecting extravascular lung water compared to chest x-ray findings, oxygenation trends, and symptomatology, however this technique is not generally used for this purpose (53).

C. METHODS

Research Objectives

1) Estimate the incidence of respiratory AEs that occur during induction therapy in pediatric AML.
2) Categorize and grade respiratory AEs that occur during the induction course.
3) Describe the temporal course of respiratory AE development during induction therapy.
4) Identify predictors of respiratory AE development during induction therapy.

Study design

A retrospective cohort study was conducted on a group of 113 pediatric patients with newly diagnosed *de novo* AML treated at a single institution. Subjects were followed from initial presentation until the completion of the first 42 days of induction chemotherapy, initiation of the subsequent chemotherapy cycle (if prior to day 42), or death from any cause. Patients underwent induction chemotherapy for *de novo* AML between March 25, 2009 and December 31, 2016 at Children's Healthcare of Atlanta (CHOA). Eligible subjects were identified through the institutional cancer registry. Electronic medical records (EMR) were retrospectively examined from the time of initial presentation until the conclusion of the follow up period. Study data were collected and managed using REDCap® electronic data capture tools hosted at CHOA.

Participants

We included all pediatric patients (age ≤ 21 years at disease onset) with *de novo* AML that underwent conventional induction I chemotherapy at a single institution in Atlanta. For the purposes of this study, *de novo* AML comprised of APL, therapy-related myeloid neoplasms, and myeloid leukemia associated with Down syndrome, in addition to those

classical AML cases (AML with recurrent genetic abnormalities, AML not otherwise specified). Exclusion criteria included relapsed AML, AML with preceding myelodysplastic syndrome, occurrence of any aspect of induction chemotherapy treatment at another institution, and use of an unconventional therapeutic approach (e.g. palliative chemotherapy, declining chemotherapy, proceeding directly to high dose chemotherapy and allogeneic bone marrow transplant).

Variables

Data were collected from CHOA EMR on a variety of independent variables and outcomes. The primary outcome of interest was the occurrence of any grade 2-5 respiratory AE at any point during the follow up period as defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE). Multiple discrete respiratory AEs could be potentially attributed to a single subject, however occurrence of a subsequent AE required complete resolution of the prior AE in terms of symptoms, oxygen/ventilation requirements, and abnormal imaging findings. AEs were ascertained by examining each subject's induction course for development of an oxygen requirement, an invasive or noninvasive ventilator requirement, beta-2 agonist use for bronchospasm, apneic events, dyspnea without oxygen or ventilatory needs, or occurrence of pleural effusion without oxygen or ventilatory needs. Each AE was then trended for start date, end date, total duration, interventions required, maximum respiratory support, and chest radiology reports. Category of AE was selected in reference to the most specific and severe classification (e.g. if a subject experiences grade 4 hypoxia, grade 4 dyspnea, and grade 4 pulmonary edema, the selected category and grade would be grade 4 pulmonary edema; if a subject experiences grade 4 hypoxia and grade 4 pulmonary edema and progresses to develop grade 4 ARDS, the selected category and grade would be grade 4 ARDS). Time-to-event was measured in days relative to the day of hospital admission.

The majority of independent variables were time independent and referred to values obtained at the time of diagnosis. Laboratory values were collected “at the time of diagnosis” as defined as the first documented evaluation occurring between the time of initial presentation until Day 1 of chemotherapy. If a value was not assessed until after initiation of chemotherapy, it was considered missing. These variables were as follows:

- age (years)
- gender
- race/ethnicity
- BMI at diagnosis (kg/m^2)
- white blood cell count (10^3 cells/mm^3)
- hemoglobin (g/dL)
- platelet count (platelets/mm^3)
- creatinine (mg/dL)
- uric acid (mg/dL)
- albumin (g/dL)
- prothrombin time (PT) (seconds)
- activated partial thromboplastin time (aPTT) (seconds)
- fibrinogen (mg/dL)
- D-dimer (ng/dL)
- comorbid cardiopulmonary disease (categorical variable referring to presence of any structural cardiac disease, previously diagnosed cardiac condition, or previously diagnosed pulmonary condition)
- pre-chemotherapy left-ventricular ejection fraction (%)
- presence of CNS disease at diagnosis

- FAB subtype (categorical variable corresponding to the subtype of AML as defined by the French-American-British system)
- peripheral blood blast percentage as identified by flow cytometry
- cytogenetic status (categorical variable corresponding to applicable cytogenetic abnormalities including t(8;21), inv(16), KMT2A abnormalities, monosomy 5, monosomy 7, and complex karyotype)
- Flt3-ITD status
- nucleophosmin (NPM) status
- CEBPA status
- occurrence of tumor lysis syndrome (TLS) (categorical variable corresponding to whether rasburicase and/or aluminum hydroxide were administered at any point during the follow up period)
- occurrence of infection at any time in the follow up period (categorical variable defined by blood culture growth of a bacterial and/or fungal organism, a positive viral respiratory panel, culture-negative sepsis, growth of an organism on endotracheal tube aspirate culture, and/or or a chest imaging report explicitly suggesting a pulmonary infectious process)
- occurrence of fluid overload at any time in the follow up period (categorical variable corresponding to administration of ≥ 3 doses of furosemide, a relative weight gain of ≥ 10% admission weight, or use of hemodialysis or continuous veno-venous hemofiltration at any point during the study period)

Several FAB morphologic subtypes at the time of diagnosis were not documented in the medical records. These undocumented cases were assigned in a post-hoc analysis by a pediatric hematopathologist using cytogenetic abnormalities and immunophenotypic characteristics (e.g. all t(8;21) cases were classified as M2, all inv16 cases were

classified as M4eo). Treatment-related AML cases were not assigned an FAB morphologic subtype as this is not commonly done in clinical practice, and were coded as missing.

Two time-dependent independent variables were additionally documented. Subjects were classified as being within a fluid overload state or infection state at each date of the follow up period. Subjects entered fluid overload status at the time of first furosemide administration if they received > 2 doses of furosemide within a 72 hour period or at the time of attaining ≥ 10% weight gain. Subjects exited fluid overload status if > 48 hours passed between furosemide doses or weight returned below the 10% threshold. Subjects entered positive infection status at the time of any fever in the context of laboratory, radiographic, or clinical infection diagnosis or, if afebrile, at the time of clinical or microbiologic infection reporting. Subjects exited positive infection status when blood culture, ETT culture, or chest imaging normalized and/or associated fever resolved for > 24 hours. If a subject experienced a respiratory AE, they were removed from the risk set from the day of AE onset until resolution of the AE.

Study size

At a type 1 error rate of 0.05 and with 80% power, we determined that we would need 112 total patients (56 in both the exposed and unexposed groups) to detect an effect size for our binary outcome between 6% incidence in the unexposed and 25% incidence in the exposed. The 6% figure was chosen as this reflects the proportion of patients on the COG AAML03P1 and AAML0531 phase 3 studies reported to have developed NCI CTCAE grade 3-5 hypoxia during induction I (4).

Statistical methods

Summary statistics were calculated to characterize the cohort. Descriptive statistics were obtained on the outcome variables, including number of subjects experiencing a respiratory AE, total number of grade 2-5 respiratory AEs and their categories, grade 3-5 respiratory AEs and their categories, and induction deaths and their causes. Subjects were divided into “respiratory AE” and “no respiratory AE” groups based on the occurrence of ≥ 1 respiratory AE. A time-to-event distribution curve was created in relation to day of initial presentation. The “respiratory AE” cases were further divided into “early” and “late” AE cases corresponding to events that occurred up until day 10 from presentation and those that occurred after day 10, respectively. Bivariate comparisons between the “respiratory AEs were obtained using Chi-square or Fisher’s exact tests for categorical variables or two-sample T-tests for normally distributed continuous variables. Multivariable analysis via logistic regression modeling was used to determine relationship between time-independent predictor variables and outcomes, incorporating statistically significant independent variables on bivariate analysis and historically significant variables documented in the literature. For survival analysis, the Kaplan-Meier method was used to estimate cumulative incidence of respiratory AEs with censoring for death from other causes as well as estimate cumulative incidence of fluid overload and infection occurrence. A Cox proportional hazard model for recurrent events was used to estimate the hazard ratio between the time-dependent independent variables and respiratory AE development.

To address missing data, multiple imputation was performed followed by regression analyses using both complete cases and multiply imputed data. If multiple imputation and complete case analysis methods yielded similar parameter estimates for predictor

variables, the missing data was determined to be missing at random and a complete case analysis was selected for the final analysis.

Two sensitivity analyses were performed. The first involved assessing the bivariate association between FAB morphology and respiratory AE development while excluding FAB M3 and M7 morphologies from the analysis. All M3 cases were APL and all APL cases were M3. The second sensitivity analysis excluded the APL and Down syndrome cases from the Cox proportional hazard model for recurrent events.

For all tests described, a p value < 0.05 was considered statistically significant. All computations were performed using SAS System v9.4 (2012, SAS Institute, Cary, NC, USA).

D. RESULTS

Patient characteristics and clinical presentation

Between March 25, 2009 and December 31, 2016, 129 pediatric patients with *de novo* pediatric AML were identified through the institutional cancer registry at CHOA. Figure 1 demonstrates the CONSORT diagram for subject eligibility. After removing subjects that did not meet the definition of *de novo* AML (n = 8), were not treated per conventional protocols (n = 2), were treated at another institution for any part of induction I (n = 4), and whose charts could not be located (n = 2), the final cohort of 113 patients meeting inclusion criteria were entered into the cohort. Table 1 provides a summary of the demographic and clinical characteristics of these subjects at the time of diagnosis. Median age at diagnosis was 8 years (range, 0-20 years). The female-to-male ratio was 3:2. The relative percentages of each race and ethnicity closely mirrored the distribution seen in the Georgia population on the whole. KMT2A abnormalities, t(8;21) positivity, inv(16) positivity, myelodysplastic changes, and Flt3 internal tandem duplications (ITD) occurred at similar frequencies when compared to the pediatric AML population overall (54, 55). Subjects were categorized into the following FAB subtypes at the time of diagnosis: 1.2% M0 (n = 1), M1 2.3% (n = 2), M2 11.6% (n = 10), M3 9.3% (n = 8), M4 or M4eo 12.8% (n = 11), M5 36.1% (n = 31), M6 1.2% (n = 1), M7 25.6% (n = 22). Of the M7 subjects, 50% (n = 11) had Down syndrome. FAB morphologic subtype was missing in 27 subjects.

Treatment, response, and follow-up

All subjects (n = 113) were either enrolled onto a COG treatment protocol or treated with conventional chemotherapy per cooperative or institutional guidelines. End-of-induction bone marrow aspirate evaluations were positive for minimal residual disease in 21 cases (19.6%).

Survival and outcome

Follow-up data were available for all 113 subjects at either Day 42 of induction I chemotherapy, at the date of initiation of subsequent chemotherapy cycle, or at the date of death from any cause. During the follow up period, 5 subjects died (4.4% induction death at days 2, 5, 19, 25, and 73 from the initiation of chemotherapy). Three of these deaths were attributed to respiratory failure in the context of invasive fungal infection with pulmonary involvement. In total, 60 subjects (53.1%) experienced 74 discrete grade 2-5 respiratory AEs. Table 1 details the NCI category and grade of each respiratory AE. 66 of these events (89.2% of all AEs) were grade 3-5. Among the respiratory AEs, 33.8% required high-flow nasal cannula (n = 4), BiPAP/CPAP (n = 4), or mechanical ventilation (n = 17) as the highest level of respiratory support. Grade 3-5 hypoxia (n = 31), grade 3-5 pulmonary edema (n = 10), and grade 2-5 pleural effusion (n = 9) accounted for 41.9%, 13.5%, and 12.2% of all respiratory AEs respectively. ARDS (n = 3) and pulmonary hemorrhage (n = 2) were relatively rare among the cohort. Figure 2 shows the distribution of time from initial presentation until respiratory AE development. Of the 74 respiratory AEs, the mean time to development was 8.6 days (SEM 1.1) with a large peak noted between days 0-7 and a smaller peak between days 14-21.

Table 2 details the differences between the AE and no AE groups. Higher median age at diagnosis (12.5 years vs 3 years, $p < .0001$), male gender ($p = .019$), increased WBC at diagnosis (82.4 10^3 cells/µL vs 38.4 x 10^3 cells/µL, $p = .007$), increased peripheral blast percentage (56.8% vs 35.1%, $p = .0004$), increased uric acid at diagnosis (5.5 mg/dL vs 3.74 mg/dL, $p = .003$), increased PT at diagnosis (17 sec vs 15.5 sec, $p = .001$), increased D-dimer at diagnosis

(3726 ng/dL vs 1566 ng/dL, p = .001), fluid overload occurrence at any time during the follow up period (p < .0001), infection occurrence at any time during the follow up period (p = .006), and tumor lysis syndrome occurrence (p = .009) were significantly associated with AE development on bivariate analysis. There was a statistically significant difference between the AE and no AE groups in regards to FAB morphology (p = .0029) with all M3 cases (n = 8) experiencing respiratory AEs and 77.3% of M7 cases (n = 17) not experiencing a respiratory AE. However, on sensitivity analysis, when M3 and M7 cases were removed from the cohort, the bivariate association between FAB morphology and respiratory AE development was not statistically significant (Supplemental Table 1).

Table 3 details the differences between early AE cases (≤ 10 days from presentation) and late AE cases (> 10 days from presentation). Infection at any point during the follow up period was associated with development of a late respiratory AE (p = .014). Statistically significant differences between the early and late AE groups were not observed in regards to age at diagnosis, gender, WBC at diagnosis, or fluid overload at any time during the follow up period.

Multivariable analysis with logistic regression was used to evaluate the associations between time-independent predictor variables and the outcome of respiratory AE. Age at diagnosis, initial WBC, initial PT, fluid overload at any time, infection at any time, and TLS were significantly associated with respiratory AE development in the bivariate analysis and were included in the final model. Initial D-dimer was linearly associated with initial PT (p < .0001) and peripheral blast percentage was linearly associated with initial WBC (p < .0001); given this covariation, D-dimer and peripheral blast percentage were not included in the

multivariable model (Supplemental Table 2). Elevated uric acid was significantly associated with TLS development (p = .0034) and was similarly excluded from the multivariable model due to covariation. The final multivariable logistic regression model is as follows:

$$\ln \frac{p(AE)}{1-p(AE)} = \beta_0 + \beta_1 AGE + \beta_2 WBC + \beta_3 PT + \beta_4 FLUID + \beta_5 INFECTION + \beta_6 TLS$$

As seen in Table 4, increased age at diagnosis (p = .0361) and occurrence of fluid overload at any time (p = .0003) were associated with respiratory AE development. Subjects with any occurrence of fluid overload were estimated to be 47.6 times more likely to experience a respiratory AE than those unexposed to the fluid overload state (95% CI 5.7-395.1, p = .003).

Survival analysis using a Cox proportional hazard model for recurrent events incorporated the same variables used in the multivariable logistic regression analysis, as well as gender. The final Cox proportional hazard model is as follows:

$$h(t) = h_0(t) e^{\beta_1 AGE + \beta_2 GENDER + \beta_3 WBC + \beta_4 PT + \beta_5 FLUID + \beta_6 INFECTION + \beta_7 TLS}$$

The results are demonstrated in Table 5. Male gender, elevated initial WBC, fluid overload status, and positive infectious status were each independently associated with increased instantaneous hazard for respiratory AE development. Specifically, fluid overload exposure was associated with respiratory AE development at an estimated 5.63 times higher rate than when not fluid overloaded (HR 5.63, 95% CI 3.42-9.29, p < .0001), infection exposure was associated with respiratory AE development at a 2.29 times higher rate than

when not infection exposed (HR 2.29, 95% CI 1.30-4.02, p = .0042), females experienced respiratory AEs at a 37.8% lower rate than males (HR 0.63, 95% CI 0.423-0.945, p = .0253), and for every increase in initial WBC by 1000 cells/μL was associated with an estimated increased rate of respiratory AE occurrence by 0.3%, each controlling for other covariates in the model (HR, 95% CI 1.000-1.005, p = .0433). When APL and Down syndrome cases were removed from the cohort, these statistically significant parameters observed on multivariable analysis via Cox proportional hazards model for recurrent events remained essentially unchanged (Supplemental Table 3).

Time-dependent Exposures

Fluid overload occurred in 33.6% of subjects (n = 38). Figure 3 depicts the total days spent in the fluid overload state for these 38 subjects, which occurred at a mean of 11.6 days (SEM 1.34) and median of 9.5 days (IQR 3-14 days). Figure 4 demonstrates the Kaplan-Meier distribution of time-to-overload state for the entire cohort. Notably, 66% of subjects survived induction without experiencing fluid overload and, of those subjects who did experience fluid overload, 55.9% did so within 24 hours of presentation. Multivariable logistic regression was performed with time-independent fluid overload status as the outcome variable and age at diagnosis and initial creatinine as the independent variables. Controlling for age at diagnosis, initial creatinine was not associated with development of fluid overload (p = .551).

Infection occurred in 39.8% of subjects (n = 45), with 56 discrete infections observed among those individuals. The subtypes of infection are demonstrated in Figure 5, with bacteremia accounting for 32.1% of infections (n = 18),

radiographic pneumonia 28.6% of infections (n = 16), disseminated fungal infection 14.3% of infections (n = 8), PCR-positive viral respiratory infections 14.3% of infections (n = 8), and culture-negative sepsis 10.7% of infections (n = 6). Figure 6 shows the Kaplan-Meier survival estimates of time-to-infection state for the entire cohort. Notably, 58% of subjects survived without experiencing infection with 38.1% of those that experienced infection doing so within 10 days and 83.3% experiencing infection within 20 days of presentation.

E. DISCUSSION

Despite ongoing advancements in diagnostic and therapeutic techniques, survival in childhood AML has remained stagnant at roughly 60-70% (2-6). While improvements in induction mortality have certainly been made, death during this early phase of therapy is still relatively frequent, treatment-related, and oftentimes preventable (5, 7-9, 11-13). The morbidities associated with AML complications include reduction in patient quality of life, increased hospital length of stay, delays in chemotherapy administration, predisposition to additional toxicity, and elevated healthcare costs. Yet to date, our understanding of the contributions of respiratory complications to morbidity and mortality in pediatric AML induction has been incomplete. To our knowledge, the analysis of this retrospective cohort provides the largest incidence data described in the literature thus far on respiratory AE development in the pediatric AML population during induction therapy, provides a clearer understanding of the patterns of respiratory AE occurrence, and identifies potentially modifiable risk factors for respiratory AE acquisition.

Respiratory AEs are more frequently observed in the first phase of *de novo* pediatric AML treatment than had been previously understood, although this prior knowledge was fairly limited (18, 20, 23, 25). In this cohort, we observed 74 total events occurring among 60 individuals, with 53.1% of subjects experiencing a grade 2-5 respiratory AE. Of the 74 respiratory AEs categorized, 89.2% (n = 66) were grade 3-5. The most recent extensive analysis of the COG AAML03P1 and AAML0531 clinical trials for *de novo* pediatric AML revealed 6% of pediatric patients developed grade 3-5 hypoxia during induction (4). While their investigation did not account for every category of respiratory AE assessed in our own cohort, it is a profoundly smaller percentage than we encountered. As a direct comparison, 27.4% of the subjects in our cohort developed grade 3-5 hypoxia during this same time course. As these subjects were

demographically similar to the patients on the aforementioned COG trials and were treated with essentially the same chemotherapy regimens, it is reasonable to conclude this disparity results largely from decreased reporting of respiratory AEs in prior analyses. As has been shown recently, reported AEs on the aforementioned COG AAML03P1 and AAML0531 trials were much lower than those ascertained through a gold standard of medical chart abstraction, with clinical trial adverse event reporting for grade 3-5 hypoxia and grade 3-5 ARDS exhibiting 17.4% and 38.5% sensitivities respectively (56).

While many of the respiratory AEs in our cohort resolved with simple supportive measures, a notable proportion resulted in mortality or substantial morbidity. In fact, of 5 deaths to occur during the induction period, 3 (60%) were attributable to a primary pulmonary pathology, either solely or in combination with other factors. Mechanical ventilation was required in 15% of all subjects and in 23% of all respiratory AEs (n = 17). ARDS (4.1% of all AEs) and pulmonary hemorrhage (2.7% of all AEs) were observed infrequently but were associated with notable morbidity and mortality.

Respiratory AEs largely occurred between days 0 and 7 from initial presentation with a second smaller peak of events occurring between days 14 and 21. This pattern suggests potentially discrete etiologies of earlier compared with later AEs. Demonstrated in the AML-BFM 87, 93, and 98 clinical trials, mortality up until day 14 occurred in conjunction with leukostasis and bleeding while deaths occurring after day 14 were largely associated with infection (11). We similarly noted that respiratory AEs occurring after day 14 were significantly associated with increased rates of infection (71.4% vs 33.3%, p = .014). While not statistically significant, we noted that 56.7% of early respiratory AEs occurred in subjects that experienced fluid overload, compared with 42.9% of late respiratory AEs (p = .351). PT (17.3 vs 16.4) and D-dimer (3816 vs

3517) values at initial presentation were also higher in early respiratory AEs, although also not statistically significant (p = .252 and .795 respectively), suggesting a potential contribution of coagulopathy in early respiratory AE development.

A number of risk factors for respiratory AE development, regardless of timing, were identified within this cohort. Most notably, controlling for other covariates, occurrence of fluid overload at any time during the follow up period resulted in a 48 times higher odds of experiencing a respiratory AE during induction (OR 47.6, 95% CI 5.73-395.1, p = .0003). For every additional year in age at the time of diagnosis, the odds of developing a respiratory at any time during induction increased by 12% (OR 1.116, 95% CI 1.007-1.236, p = .0361). Being in the fluid overload state at any moment in time was associated with a 5.6 times higher instantaneous hazard for respiratory AE development (HR 5.63, 95% CI 3.42-9.29, p < .0001). Infection exposure was estimated to be associated with respiratory AE development at a 2.3 times higher rate than those not exposed to infection, controlling for fluid overload status and other risk factors at the time of diagnosis (HR 2.29, 95% CI 1.30-4.02, p = .0042). Females experienced respiratory AEs at an estimated 38% lower rate than males, holding age, initial WBC, initial PT, fluid overload exposure, infection exposure, and TLS status constant (HR 0.62, 95% CI 0.42-0.95, p = .0253). Finally, for every increase in initial WBC by 1000 cells/μL, the rate of respiratory AE occurrence were estimated to increase by 0.3%, again controlling for other covariates (HR 1.003, 95% CI 1.000-1.005, p = .0433). While this increase may seem minor, the mean initial WBC was 82,400 cells/μL in our respiratory AE group and 38,400 cells/μL in our no respiratory AE group, a difference of 44,000 cells/μL on average between the two groups. To further put in perspective, 0.3% increase per 100 cells/μL translates to a 13.2% increase per 44,000 cells/μL. When APL and Down syndrome cases were removed from the cohort, the statistically significant parameters

observed on multivariable analysis via Cox proportional hazards model for recurrent events remained essentially the same. Additionally of note, on bivariate analysis, when M3 and M7 cases were removed from the cohort, FAB morphology was not associated with respiratory AE development and, as such, FAB morphology was not included in the multivariable analyses.

Although age and gender at diagnosis cannot be altered, fluid overload, infection, and WBC at diagnosis are conceivably modifiable risk factors. Fluid overload is not listed among the NCI CTCAE adverse events in the recent 2017 update and is infrequently emphasized in the pediatric oncology literature. However, in other pediatric conditions, including sepsis (29) and acute renal failure (30), fluid overload status has been associated with respiratory AE development, deterioration, and overall worse outcomes. We noted fluid overload in one third of our subjects (n = 38), with fluid overloaded subjects averaging 11.6 days within the fluid overload state. Of particular interest, on Kaplan-Meier survival analysis among all subjects, the estimated probability of entering into the fluid overload state within 24 hours of presentation was 0.19. Several management strategies for treatment and prevention of fluid overload have been explored. In a small cohort of pediatric stem cell transplant recipients with acute renal failure, a fluid overload prevention strategy using furosemide and low-dose dopamine and treatment strategy using renal replacement therapy was enacted, with all survivors maintaining euvolemia but 60% (n = 9) of the deaths occurring in the context of fluid overload (30). Additionally of note, the Fluid and Catheter Treatment Trial (FACTT) was a multicenter prospective randomized controlled trial that compared use of liberal versus conservative fluid management approaches toward adult patients with ARDS. By maintaining a conservative, net neutral fluid balance over a 7 day period, survival was significantly improved and days on the ventilator were significantly reduced (31).

The most recent pediatric guidelines on TLS prevention and management recommended ample hydration and prophylactic rasburicase use in patients at high risk for TLS development, hydration and either allopurinol or rasburicase use in intermediate risk patients, and aggressive hydration with rasburicase and diuresis as management for those patients with overt TLS and hyperuricemia (50). Within this risk stratification system, any AML patient with a WBC ≥ 100 x 10^3 cells/µL is considered high risk for TLS and any AML patient with a WBC ≥ 25 x 10^3 cells/µL and < 100 x 10^3 cells/µL or with any WBC if LDH is ≥ 2 times the upper limit of normal is considered intermediate risk for TLS (50). In our cohort, 48.7% of subjects (n = 55) presented with a WBC ≥ 25 x 10^3 cells/µL, yet 28.2% of subjects that experienced fluid overload presented with a WBC < 25 x 10^3 cells/µL, suggesting that many subjects at low risk for TLS and leukostasis are nevertheless being provided excessive IV fluids. Yet evidence suggests even those patients at high risk for TLS may not require high volumes of fluids, particularly now that rasburicase use has become so commonplace. In the era prior to widespread rasburicase use for pediatric acute leukemia at high risk for TLS, clinical TLS (defined as laboratory TLS with either renal dysfunction, leukostasis complications, or arrhythmia) occurred in roughly 13% of children with hyperleukocytosis at leukemia diagnosis (57). In 2001, Pui et al detailed 131 newly diagnosed pediatric leukemia or lymphoma patients at risk for TLS who were provided rasburicase during induction chemotherapy, noting normalization of serum creatinine by day 6 of treatment, no cases requiring dialysis, and no cases with serious TLS symptoms (58). Given the increased availability and high success rates of rasburicase as a hyperuricemia reduction agent, it may be reasonable to reassess our widely instituted practices on fluid management in pediatric patients at risk for TLS or experiencing TLS.

In the context of prolonged myelosuppression during AML induction, infection is a frequent and oftentimes life threatening occurrence, particularly from a pulmonary perspective (23, 24, 32). Pulmonary infections represented 36.5% of all clinically and/or microbiologically documented infections occurring during induction in the BFM-2004 clinical trial *de novo* pediatric AML (24). We noted a similar incidence of clinically and microbiologically documented infections as well, with pneumonia (n = 16), PCR-positive viral respiratory infections (n = 8), and disseminated fungal disease (n = 8) accounting for 28.6%, 14.3%, and 14.3% of infections in our cohort respectively. Additionally, the probability among all subjects of experiencing infection within 10 days of admission was estimated at 0.16 and the probability of experiencing infection within 20 days of presentation was estimated at 0.35. Efforts to better prevent and manage infection in this patient population have been ongoing, with notable improvements in outcomes occurring as a result of amended supportive care protocols (15). Antimicrobial prophylaxis and neutropenic fever antimicrobial strategies vary widely from institution to institution, although childhood AML induction typically features some form of antifungal prophylaxis, prophylaxis against *Pneumocystis jirovecii*, and broad spectrum Gram-positive and Gram-negative coverage for fever and therapeutic anti-mold coverage for prolonged fever (32). Fluoroquinolone, cefepime, vancomycin, and teicoplanin antibiotic prophylaxis have all shown various degrees of efficacy in adult and pediatric AML populations in reducing neutropenic fever episodes, decreasing hospital length of stay, decreasing frequency of pulmonary infections, and reducing incidence of *Streptococcus viridans* bacteremia (33-38). However these agents are not typically incorporated into standardized protocols for this patient population, largely due to concerns for antibiotic resistance and failure to show improvements in infection-related mortality (39-40). Additional proposals such as granulocyte-colony stimulating factor (G-CSF) to improve neutrophil recovery (59) and gut decontamination to reduce Gram negative bacterial

translocation (60) have not been demonstrated to decrease incidence of neutropenic fever, microbiologically-documented infections, or infection-related mortality in childhood AML induction. Development of a standardized antimicrobial prophylaxis and treatment protocol targeting yeast, mold, and *Streptococcus viridans* should be investigated in regards to decreasing the incidence and severity of respiratory AEs and overall mortality in this patient population.

Pulmonary leukemic involvement can occur in the presence or absence of hyperleukocytosis (17-20). Within our cohort, the instantaneous hazard of developing a respiratory AE increased by 0.3% with each increase in initial WBC by 1000 cells/μL, controlling for other risk factors (HR 1.003, 95% CI 1.000-1.006, p = .0448). Historic techniques for cytoreduction, including leukapheresis and hydroxyurea, have unfortunately not successfully reduced early mortality in AML hyperleukocytosis, as demonstrated in the most recent systematic review and meta-analysis of pediatric and adult patients (41). As such, swifter initiation of induction chemotherapy in patients with suspected pulmonary leukemic involvement should be explored.

In regards to determining the underlying etiology of respiratory AEs in pediatric AML induction, further research is necessary. Leukemia-specific lung involvement is difficult to confirm on imaging, with pulmonary leukostasis demonstrating either normal chest imaging nonspecific radiologic abnormalities and ALP typically coinciding with a multilobar pneumonitis (17, 20). PLI has been shown to exhibit characteristic CT findings, such as infiltration tracking the peribronchovascular lymphatic vessels (61), however chest CT imaging is rarely performed on children at the time of leukemia diagnosis and is typically reserved for prolonged neutropenic fever that can occur well over a week following initiation of chemotherapy. Lung ultrasound is highly sensitive for detecting extravascular lung water consistent with pulmonary edema, however this is not

frequently used in the pediatric population (53). Given the absence of universally utilized diagnostic techniques for ascertaining respiratory AE etiology in this population, much of the determination must be made based on temporal factors (e.g. symptom onset prior to chemotherapy initiation; symptom onset with neutropenic fever) (62). We propose using a multiple rater system for ascertainment of respiratory AE etiology. This process could be invaluable in providing more conclusive evidence as to the cause of respiratory AEs at various points in the AML induction course and how the presence of risk factors relates to these particular etiologies.

This study had several advantages, including the use of a clinically relevant research question, assessment of modifiable risk factors, and evaluation of a generalizable childhood AML cohort. Our sample size was sufficient to achieve adequate power for detecting differences between exposure groups in regards to fluid overload, infection, gender, age, and WBC at diagnosis. Additionally, we developed an objective method for manual data abstraction that can be used for future cohorts.

In terms of limitations, as a retrospective study, there are inherent difficulties in proving causal associations and controlling for unmeasured and overlooked confounders. Missing data were certainly noted, however data were determined to be missing in an arbitrary pattern, supporting use of complete cases in the final analysis. We used a single data abstractor, which places the study at risk for potential reviewer bias. Finally, our definitions of fluid overload and infection are potentially contentious. Definitions of fluid overload are highly variable throughout the adult and pediatric literature, however almost universally involve some measure of weight gain in relation to baseline. Yet even serial weights have been shown to be inaccurate in terms of determining fluid overload status, as weights in critically ill children can be difficult to frequently and accurately obtain, discrepant scales and weighing techniques are often used between one hospital

unit and another, and decreases in muscle and fat body content while critically ill can potentially disguise fluid gain (52). Definitions of infection in the pediatric oncology literature typically focus on microbiologically-defined infections (e.g. positive organism on blood culture), clinically-defined infections (e.g. culture negative sepsis), and fever without a source requiring antibiotic management. For the purposes of this study, we focused on a select group of microbiologically-defined infections (positive blood culture, positive viral PCR, positive ETT aspirate) and clinically-defined infections (positive chest imaging report, culture negative sepsis), omitting incidents of fever without a source or non-pulmonary infections (e.g. skin/soft tissue, urinary tract, gastrointestinal).

To utilize these results, further explore risk factors for respiratory AE development in pediatric AML, and assess the impact of these events, we recommend several future directions. We propose proceeding with a net-neutral fluid balance goal for newly diagnosed AML patients at low risk for TLS with consideration of a net-neutral fluid balance for all AML patients who receive rasburicase for TLS prophylaxis. We also propose enacting scheduled airway clearance and early mobilization in all pediatric AML inpatients to prevent atelectasis development. It may be beneficial to explore leukemic blast-specific data using initial peripheral blood flow cytometric analysis including immunophenotype, adhesion marker mean fluorescence intensity, and blast forward scatter. If particular blast characteristics regarding size and adhesion marker presence confer a higher risk of early respiratory AE development, it may be reasonable to propose an alternate supportive care strategy for patients exhibiting those blast phenotypes. Finally, using this manually extracted data as a gold standard, we propose exploring the use of natural language processing (NLP) of the unstructured language, lab value, and vital sign data within the EMR to detect, categorize, and grade respiratory AEs with increased efficiency and noninferior accuracy.

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G. TABLES / FIGURES

Figure 1: CONSORT diagram demonstrating subject eligibility

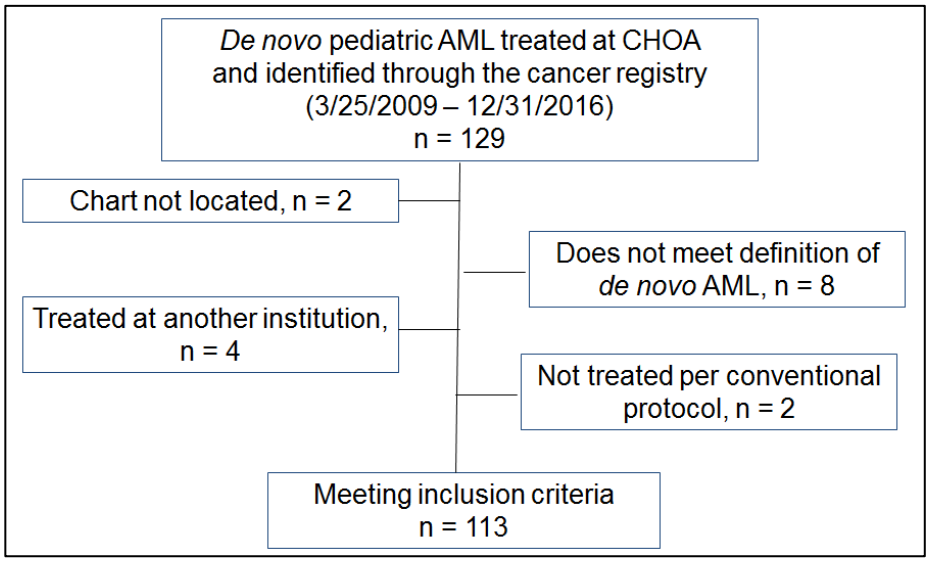


Table 1: NCI CTCAE category and grade for respiratory AEs

Parameters	Results (n = 74 events)	
Category, N (%)	Grade 2 8 (10.8)	Grade 3-5 66 (89.2)
Hypoxia	0	31 (47.0)
Pulmonary edema	0	10 (15.2)
Pleural effusion	3 (37.5)	6 (9.1)
Dyspnea	3 (37.5)	5 (7.6)
Apnea	0	4 (6.1)
ARDS	0	3 (4.5)
Pulmonary hemorrhage	0	2 (3.0)
Retinoic acid syndrome	1 (12.5)	2 (3.0)
Bronchospasm / laryngospasm	1 (12.5)	2 (3.0)

Figure 2: Time-to-event distribution from initial presentation

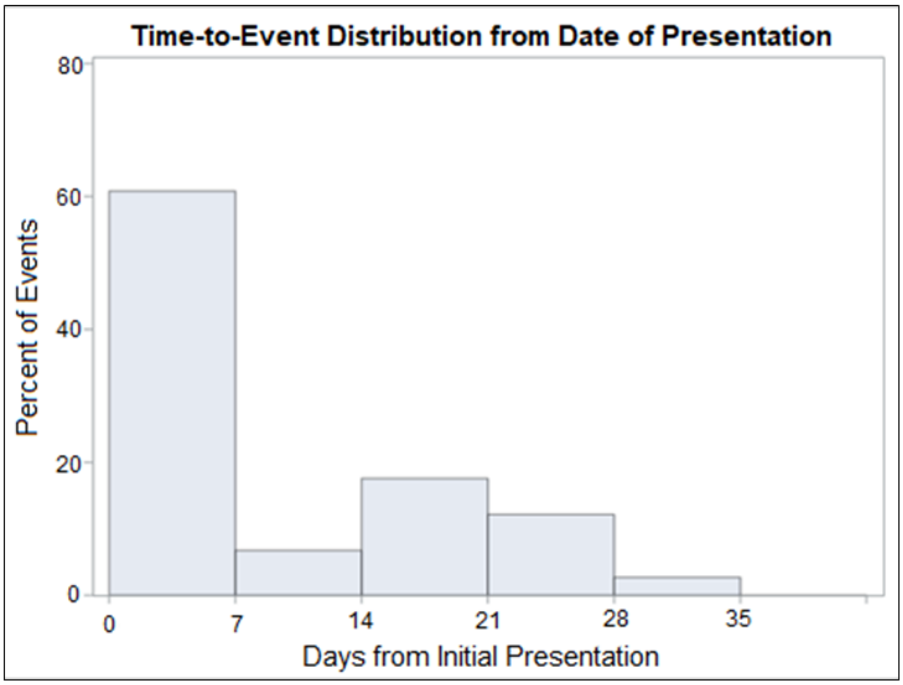


Table 2: Bivariate analysis of respiratory AE vs no respiratory AE groups

Parameters	Results (n = 113)		
	Respiratory AE 60 (53.1)	No Respiratory AE 53 (46.9)	p-value
Demographics			
Age at diagnosis, Median (range)	12.5 years (0-20)	3 years (0-17)	<.0001*
Gender, N (%)			.019*
Female	30 (50)	38 (71.7)	
Male	30 (50)	15 (28.3)	
Race/ethnicity, N (%)			.233
White, non-Hispanic	30 (50.9)	30 (56.6)	
Black, non-Hispanic	24 (40.7)	13 (24.5)	
Hispanic	2 (3.4)	6 (11.3)	
Asian or PI	2 (3.4)	3 (5.7)	
Native American	1 (1.7)	1 (1.9)	
Prior cardiopulmonary disease, N (%)	8 (13.3)	5 (9.43)	.517
Initial EF, Mean (SEM)	67.3 (0.93)	69.8 (1.08)	.073
Laboratory values at diagnosis, Mean (SEM)			
WBC (10^3 cells/μL)	82.4 (12.8)	38.4 (9.4)	.007*
Peripheral blasts (%)	56.8 (4.0)	35.1 (4.6)	.0004*
Hgb (g/dL)	7.75 (0.32)	8.25 (0.34)	.285
Platelets (10^3 platelets/mm^3)	69.5 (9.0)	76.1 (10.5)	.0875
Creatinine (mg/dL)	0.95 (0.35)	0.44 (0.03)	.171
Albumin (g/dL)	3.65 (0.08)	3.75 (0.08)	.370
Uric acid (mg/dL)	5.48 (0.51)	3.74 (0.20)	.003*
PT sec	17.0 (0.30)	15.5 (0.32)	.001*
D-dimer (ng/dL)	3726.2 (488.4)	1565.7 (397.9)	.001*
Treatment related variables, N (%)			
Fluid overload	38 (63.3)	1 (1.9)	<.0001*
Infection	31 (51.7)	14 (26.4)	.006*
Tumor lysis syndrome	14 (23.3)	3 (5.7)	.009*
FAB morphology, N (%)			.0029*
M0	1 (1.7)	0 (0)	
M1	0 (0)	2 (3.8)	
M2	7 (11.7)	3 (5.7)	
M3	8 (13.3)	0 (0)	
M4 or M4eo	7 (11.7)	4 (7.5)	
M5	18 (30.0)	13 (24.5)	
M6	0 (0)	1 (1.9)	
M7	5 (8.3)	17 (32.1)	
Missing	14 (23.3)	13 (24.5)	

Table 3: Bivariate analysis of early versus late respiratory AEs

Parameters	Results (n = 74)		
	Early Respiratory AE 60 (81.2)	Late Respiratory AE 14 (18.9)	p-value
Demographics			
Age at diagnosis, Median (range)	13 years (0-20)	15.5 years (0-17)	.257
Gender, N (%)			
Female	31 (51.7)	6 (42.9)	.553
Male	29 (48.3)	8 (57.1)	
Laboratory values at diagnosis, Mean (SEM)			
WBC (10^3 cells/μL)	88.9 (13.9)	90.0 (26.2)	.972
PT sec	17.3 (0.34)	16.4 (0.51)	.252
D-dimer (ng/dL)	3816 (482)	3517 (1149)	.795
Time-dependent treatment related variables, N (%)			
Fluid overload	34 (56.7)	6 (42.9)	.351
Infection	20 (33.3)	10 (71.4)	.014*

Table 4: Multivariable logistic regression analysis (respiratory AE vs no respiratory AE)

Parameters	Respiratory AE (n = 113)	
	aOR (95% CI)	p-value
Age at diagnosis (years)	1.116 (1.007-1.236)	.0361*
Initial WBC (10^3 cells/μL)	1.004 (0.995-1.013)	.3462
Initial PT (sec)	0.874 (0.618-1.236)	.4461
Fluid overload at any time		
Yes	47.59 (5.73-395.07)	.0003*
No	1.00	
Infection at any time		
Yes	1.881 (0.59-6.05)	.2888
No	1.00	
Tumor lysis syndrome		
Yes	2.564 (0.419-15.686)	.3081
No	1.00	

Table 5: Multivariable survival analysis with Cox PH model for recurrent events (respiratory AE vs no respiratory AE)

Parameters	Respiratory AE (n = 113)	
	aHR (95% CI)	p-value
Age at diagnosis (years)	1.016 (0.977-1.057)	.4152
Gender		
Female	0.632 (0.423-0.945)	.0253*
Male	1.00	
Initial WBC (10^3 cells/μL)	1.003 (1.000-1.005)	.0433*
Initial PT (sec)	1.002 (0.887-1.132)	.9741
Fluid overload at any time		
Yes	5.63 (3.42-9.29)	<.0001*
No	1.00	
Infection at any time		
Yes	2.29 (1.30-4.02)	.0042*
No	1.00	
Tumor lysis syndrome		
Yes	1.365 (0.805-2.314)	.2477
No	1.00	

Figure 3: Survival analysis: time to fluid overload state

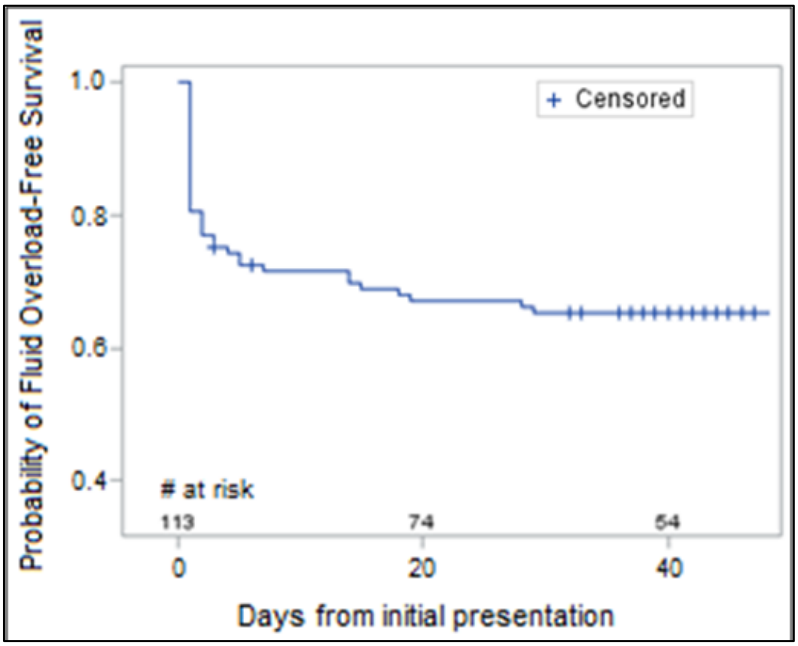


Figure 4: Total days in fluid overload state

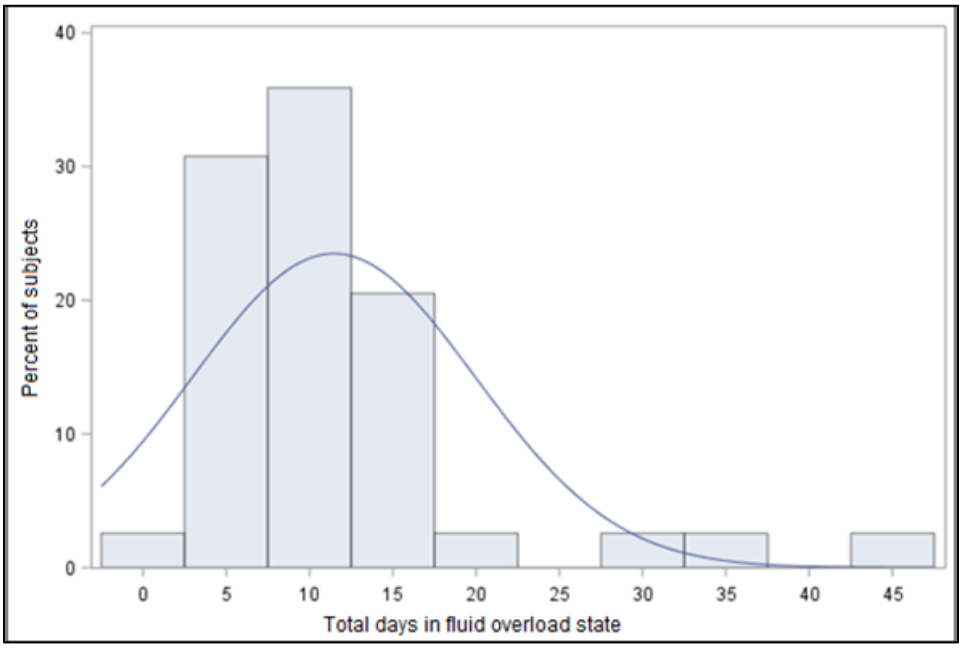


Figure 5: Infection subtypes

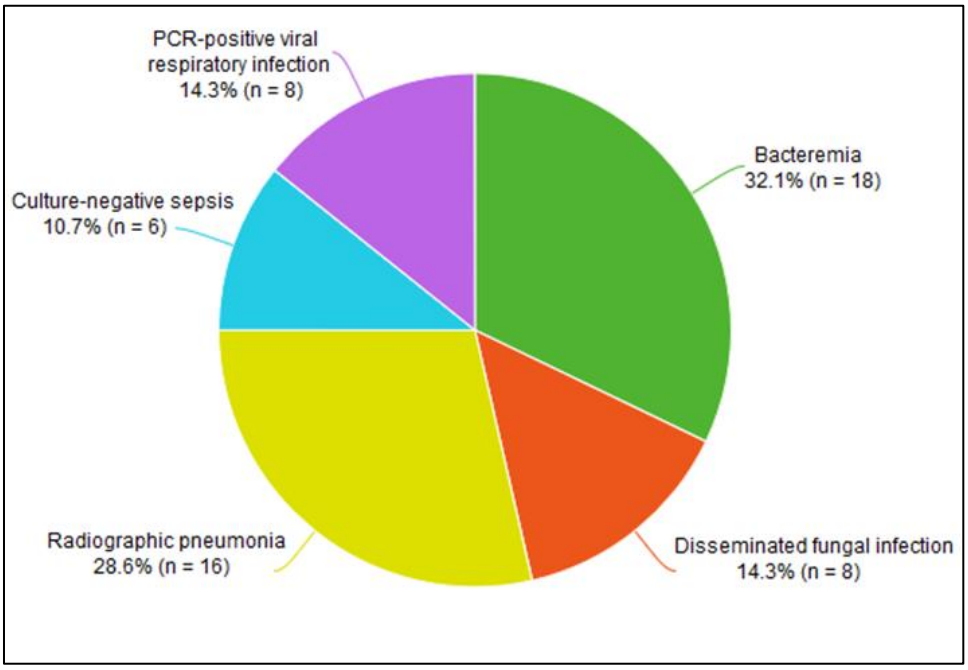
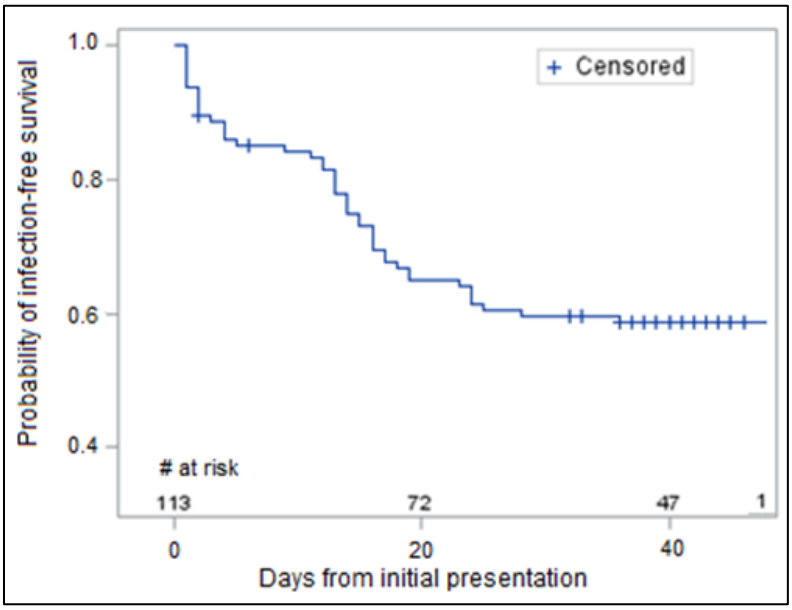


Figure 6: Survival analysis: time to infection state



Supplemental Table 1: Sensitivity analysis: bivariate analysis of respiratory AE vs no respiratory AE excluding M3 and M7 cases

Parameters	Results (n = 83)		
	Respiratory AE (n = 47)	No Respiratory AE (n = 36)	p-value
FAB morphology, N (%)			
M0	1 (2.13)	0 (0)	
M1	0 (0)	2 (5.6)	
M2	7 (14.9)	3 (8.3)	
M4 or M4eo	7 (14.9)	4 (11.1)	.647
M5	18 (38.3)	13 (36.1)	
M6	0 (0)	1 (2.8)	
Missing	14 (29.8)	13 (36.1)	

Supplemental Table 2: Covariation between initial PT and initial D-dimer. Covariation between initial WBC and peripheral blast percentage.

Parameters	Results (n = 112)	
	Initial PT	Initial D-dimer
Initial PT	1.000 n = 110	r = 0.455 p < .0001 n = 104
Initial D-dimer	r = 0.455 p < .0001 n = 104	1.000 n = 104

Parameters	Results (n = 112)	
	Initial WBC	% Peripheral Blasts
Initial WBC	1.000 n = 114	r = 0.579 p < .0001 n = 113
% Peripheral Blasts	r = 0.579 p < .0001 n = 113	1.000 n = 113

Supplemental Table 3: Sensitivity analysis: multivariable survival analysis with Cox PH model (respiratory AE vs no respiratory AE) excluding M3 and Down syndrome cases

Parameters	Respiratory AE (n = 113)	
	aHR (95% CI)	p-value
Age at diagnosis (years)	1.017 (0.973-1.064)	.4483
Gender		
Female	0.583 (0.374-0.907)	.0168*
Male	1.00	
Initial WBC (10^3 cells/μL)	1.003 (1.000-1.006)	.0448*
Initial PT (sec)	1.003 (0.881-1.143)	.9602
Fluid overload at any time		
Yes	5.138 (3.06-8.62)	<.0001*
No	1.00	
Infection at any time		
Yes	2.51 (1.34-4.69)	.0039*
No	1.00	
Tumor lysis syndrome		
Yes	1.435 (0.864-2.385)	.163
No	1.00	