Leukemia Research 62 (2017) 51–55

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Outcomes and changes in code status of patients with acute myeloid leukemia undergoing induction chemotherapy who were transferred to the intensive care unit

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ARTICLE INFO

Keywords:
Acute myeloid leukemia
ICU
Code status

ABSTRACT

Patients with Acute Myeloid Leukemia (AML) have compromised marrow function and chemotherapy causes further suppression. As a result complications are frequent, and patients may require admission to the intensive care unit (ICU). How codes status changes when these events occur and how those changes influence outcome are largely unknown. Outcomes for adult patients with AML, undergoing induction chemotherapy, and transferred to the ICU between January 2000 and December 2013 were analyzed. 94 patients were included. Median survival was 1.3 months. At 3 and 6 months overall survival (OS) was 27% and 18% respectively. Respiratory failure was the most common reason for transfer to ICU (88%), with 63% requiring mechanical ventilation at transfer. Other reasons included: cardiac arrest (18%), septic shock (17%), hypotension (9%), and acute renal failure (9%). The most frequent interventions were mechanical ventilation in 85%, vasopressors in 62%, and hemodialysis in 30%. Following transfer 55 patients (58%) had a change in code status. Overall, 46 patients (49%) changed from Full Code (FC) to Comfort Care (CC), 7 (7%) from FC to Do Not Resuscitate (DNR), and 2 (2%) from DNR to CC. For the entire cohort, ICU mortality (IM) was 61% and hospital mortality (HM) was 71%. For FC or DNR patients, IM was 30% and HM was 41%. For CC patients, IM was 90% and HM was 100%. Overall, 27 patients (29%) survived to discharge. Of those discharged, 22 (81%) were alive at 3 months and 17 (63%) were alive at 6 months. In conclusion, patients that required ICU admission during induction chemotherapy have a poor prognosis. Code status changed during the ICU stay for the majority of patients and always to a less aggressive status.

1. Introduction

Acute Myeloid Leukemia (AML), a hematologic malignancy characterized by the clonal proliferation of myeloblasts, is the most common acute leukemia in adults and is uniformly fatal without treatment [1]. The initial phase of treatment is referred to as remission induction therapy. For nearly 40 years, the use of an anthracycline with cytarabine has constituted the backbone of remission induction therapy [2]. The goal of treatment is to obtain a rapid restoration of normal hematopoiesis without morphological evidence of residual leukemia termed a complete remission (CR). However, both AML and its therapies can compromise bone marrow function resulting in prolonged periods of neutropenia and thrombocytopenia putting patients at risk for infectious complications and hemorrhages, respectively. As a result, these complications can lead to end-organ damage or multi-organ system failure requiring transfer to the intensive care unit (ICU). ICU admissions in this setting are felt to be associated with high mortality rates leading some practitioners to view these transfers as potentially inappropriate therapy. Few studies have investigated ICU intervention in AML patients specifically during induction therapy.

Sharing management decisions among oncologists and ICU physicians may be a source of conflict as the short-term prognostic impact of organ dysfunction may overshadow the overall AML prognosis [3]. Before the patient is admitted to the ICU, a decision whether or not to

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http://dx.doi.org/10.1016/j.leukres.2017.09.017
Received 10 February 2017; Received in revised form 16 August 2017; Accepted 24 September 2017
Available online 27 September 2017
0145-2126/

transfer the patient must be made considering various factors including the reversibility of the acute condition, prospect of long-term survival, facility limitations, and skill set availability. Acutely ill AML patients are a heterogeneous group and as a result vastly different outcomes have been observed in both the short-term and long-term survival between individual patients. In order to better guide treatment decisions, it would be useful to identify clinical factors that can predict favorable outcomes. Short-term mortality is usually associated with the characteristics of the acute illness and the use of vasopressors or mechanical ventilation may hold prognostic significance. Long-term prognosis appears to be associated with general AML prognostic factors including cytogenetics, age, and response to treatment [4]. Some studies have shown that patients with AML who survive the ICU have the same continuous complete remission rates and long-term survival as non-ICU patients with AML [3]. How patients and their families integrate this complex information and what decisions are made regarding the desire for continued aggressive care are largely unreported.

The purpose of this retrospective study was to describe changes in codes status, outcomes and prognostic factors for a group of patients with AML all undergoing induction chemotherapy admitted to the intensive care unit in a large academic medical center. We also describe the reasons cited for transfer, the interventions made during the stay, and disposition from the ICU.

2. Patients and methods

2.1. Patients

This retrospective study was approved by the Institutional Review Board of Wake Forest University. We reviewed the medical records for all patients with the diagnosis of non-APL AML who were transferred to the ICU between January 01, 2000 and December 31, 2013 at Wake Forest University Baptist Medical Center. Data was collected by chart review. Inclusion criteria were: Age > 18, not APL, and admission to the ICU during initial induction chemotherapy. The majority of cases that were excluded were admissions for acute illness, patients with APL or for re-induction/salvage chemotherapy. As the purpose of the study was to assess the change in code status of AML patients initially admitted to the leukemia service patients that were admitted to the ICU upon hospital admission and later received induction therapy were not included in this study.

Patient characteristics reviewed included age, number of comorbidities, social history, physical exam, baseline labs on admission, history of antecedent hematologic disorder, and cytogenetic risk group. Comorbidities captured included congestive heart failure, coronary artery disease, cerebrovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, renal dysfunction, previous cancer, depression, osteoporosis, rheumatologic disease (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjogren's disease), cognitive impairment, venous thromboembolism (deep venous thrombosis including venous catheter associated, pulmonary embolism), cardiac valve disease, and cirrhosis. Labs on the day of ICU transfer were also obtained. Review of cytogenetic status included karyotypes taken from bone marrow biopsy samples taken at initial diagnosis. Karyotypes were divided into favorable karyotypes [t(8;21), t(16;16) or i16], unfavorable karyotypes [−5, del(5q), −7, del(7q), complex karyotype (3 or more abnormalities), or 11q23 translocation], and intermediate (all other abnormalities) as described by the European LeukemiaNet (ELN) [5].

Terminologies for code status at our institution included four options. Full Code, is a term defined as the use of every effort to sustain life. Do Not Resuscitate-full scope of treatment (DNR-Full), a term meaning do not initiate cardiopulmonary resuscitation (CPR) or advanced cardiac life support (ACLS). DNR-limited scope of treatment (DNR-Limited), is a term indicating not to initiate CPR, ACLS, or intubation sequence for mechanical ventilation. Both DNR-Full and DNR-Limited allow for full resuscitative medical therapy including the use of vasopressors, antibiotics, and potentially renal replacement therapy. Comfort Care, is a term to identify the use of interventions that will sustain comfort for the patient as they transition to end of life. This terminology was not uniform throughout the timeframe of this study. Because of the change over time, our analysis was done using three terminologies as follows: Full Code, DNR (included DNR-Full and DNR-Limited where differentiated), and Comfort Care.

2.2. Objectives

The primary objective of the study was to describe overall survival and code status for the cohort. Secondary objectives included 3 month and 6 month survival, ICU survival, hospital mortality, reason for ICU transfer, duration of ICU stay, disposition after hospitalization, requirement of intubation/mechanical ventilation, requirement of vasopressors, requirement of renal replacement therapy, and requirement of surgical intervention.

2.3. Response assessment

Overall survival was defined as the time from the date of diagnosis to the date of death. If patient was alive at the date of last contact, he/she was censored at that time point. ICU survival was defined as the time from ICU admission to date of death and time from ICU discharge to date of death. The criteria used to define response following induction chemotherapy were outlined by Dohner et al. [6] including CR (neutrophils > 1000/μl, platelets > 100,000/μl, and bone marrow blasts < 5%) and CRi (all marrow criteria of CR but with only either complete platelet or neutrophil recovery).

2.4. Statistical analysis

Descriptive statistics were used to describe the characteristics of the sample. Median overall survival (OS) of the sample will be calculated using Kaplan-Meier estimation. A log rank test will be used to evaluate differences between predictor variable categories for OS. A Cox proportional hazards model will be used to evaluate a multivariate OS model. Chi-square tests or Fisher's exact tests will be used to evaluate differences of predictor variables for the secondary outcomes of 30 day survival, 60 day survival, use of intubation/mechanical ventilation, new location after hospital discharge, reason for ICU transfer, requirement of vasopressors, and need of renal replacement therapy. A multivariate logistic regression model will also be used for these outcomes which are binary if multiple independent predictors show association with the outcomes.

3. Results

Of 246 cases reviewed, 94 met inclusion criteria. Age greater than 60 at the time of diagnosis included 69 patients (73.4%) and age 60 years or less included 25 patients (26.6%). There were 51 (54.3%) males and 43 (45.7%) females. The majority of patients were white (91.5%). 60 patients (63.8%) had de novo AML, 26 patients (27.7%) had secondary AML, and 8 patients (8.5%) had therapy related AML. 23 patients (24.5%) had zero comorbidities, 24 patients (25.5%) had one comorbidity, 23 patients (24.5%) had 2 comorbidities, and 24 patients (25.5%) had 3 or more comorbidities (Table 1).

Respiratory failure was the most frequent reason for transfer to ICU and was seen in 83 patients (88%) with 59 patients (63%) requiring mechanical ventilation at the time of transfer. Other reasons for ICU transfer included: cardiac arrest in 17 patients (18.1%), septic shock in 16 patients (17%), hypotension of unclear origin in 8 patients (8.5%), acute renal failure in 8 patients (8.5%), uncontrolled bleeding in 2 patients (2.1%) and decompensated heart failure in 1 patient (1.1%). Patients may have had more than one of these indications at the time of