Expectations of Serious Adverse Events at the End of Life of Patients With Acute Myeloid Leukemia Who Receive Salvage Therapy

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Abstract

Patients with acute myeloid leukemia (AML) and refractory disease receive investigational therapies within 2 months of their death. Baseline expectations of serious adverse events (AEs) need to be established to compare the combined effects of disease progression and expected complications of the AML therapy with those of the new drugs. We observed similar profiles of AEs in patients treated with investigational or conventional drugs.

Background: Patients with AML and refractory disease receive investigational therapies within 2 months of their death. The attribution of serious AEs in this phase to disease progression vs. drug toxicity is tenuous. We aimed to determine the incidence of serious AEs in the last 2 weeks of life of patients with refractory-relapsed AML undergoing salvage therapy (ST). **Patients and Methods:** Adults who received ST from September 2010 to December 2011 were evaluated. Data collected included incidence of serious AEs, type of ST, medical complications, length of hospital stay, and Intensive Care Unit stays, organ dysfunctions, and use of life support therapies. **Results:** A total of 122 patients received ST. Most 64 patients (52%) received intensive chemotherapy; 39 patients (32%) had single investigational drug therapies, and 19 patients (16%) received therapy with hypomethylating agents. Common complications were pneumonia (82%), disseminated intravascular coagulopathy 72 patients (59%), and septic shock 60 patients (49%). Notable complications included: acute respiratory failure justifying invasive mechanical ventilation in 60 patients (42%), renal failure requiring dialysis in 33 patients (27%), atrial fibrillation in 37 patients (30%), and prolonged prothrombin time (grade 3) in 68 patients (56%). There was no difference in the incidence of these complications by type of ST. **Conclusions:** Baseline expectations of serious AEs at the end of life of patients with AML undergoing ST were established. The AE profiles of new investigational interventions or therapies could be compared with what would be expected in such circumstances from the combined effect of disease progression, expected complications of the AML therapy, and therapies delivered in previous historical contexts.

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Introduction

With modern intensive combination chemotherapy, patients with acute myeloid leukemia (AML) achieve complete remission rates of 50% to 80% and have long-term survival rates of 5% to 80%.[1,2] Despite these improvements, treatment of patients diagnosed with AML remains a challenge because good outcomes are strongly dependent on several patient- and disease-related factors including patient age, performance status, comorbidities, cytogenetic and molecular abnormalities, and the types of therapy used.[3] Most patients relapse and require salvage therapies. Standard salvage therapies include cytarabine-based combinations but patients whose leukemia progresses while using standard therapies often consider investigational therapies.[4] A critical component in evaluating the efficacy of investigational drugs is to determine the toxicities attributable to the new treatment vs. complications anticipated from disease progression and from AML-associated cytopenias.[5] Knowledge of the expected incidence of these events can be used as

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a benchmark for baseline expectations against which the incidence of serious adverse events (AEs) with new investigational therapies could be compared. This, for example, could be very useful to determine the increased risk of atrial fibrillation, cardiopulmonary toxicities, hepatic toxicities, renal failure, seizures, or any such life-threatening or serious AE, to dissect in future studies whether they are truly caused by the new regimen or whether they are in line with the expected incidence of side effects during the terminal care of patients with AML. The purpose of this analysis was to establish the baseline expectations of such serious AEs at the end of life of patients with AML.

Patients and Methods

Study Group

All adults with AML receiving salvage therapy under the care of the Department of Leukemia at The University of Texas M.D. Anderson Cancer Center between September 1, 2010, and December 25, 2011 were included in this study. Patients were selected if they had a confirmed diagnosis of AML and had died in the hospital while receiving salvage therapy in clinical trials. The inclusion/exclusion criteria of the clinical trials was similar and patients had adequate Zubrod performance status (0-2), good organ functions, and were mentally competent to consent to participate in the clinical trial and to make medical decisions. We focused on the last 2 weeks before death in collecting data of serious AEs, complications, and end of life issues. The study received approval from the Institutional Review Board, and consisted of retrospective analysis and chart review of these patients.

Information collected included age, sex, characteristics of the leukemia, salvage therapy, dates of hospitalization, clinical course, and complications including organ failures, and use of life supportive infrastructures such as ventilators, or dialysis. Salvage therapeutic attempts were considered in the following categories: intensive chemotherapy, investigational single-agent therapies, and hypomethylating agents. The number of salvage attempts and the date of last salvage therapy were also recorded.

Reasons for hospitalizations were collected and included in the following broad categories: febrile neutropenia, documented infections, dyspnea/hypoxemia, pain, or others. The latter category included patients admitted for renal failure, altered mental status/confusion, cardiovascular events, hepatic failure or dysfunction, or bleeding. Additional information collected included: use of the Intensive Care Unit (ICU); invasive mechanical ventilation; need for dialysis; use of 2 or more vasopressors; abnormal chemistries, blood counts and coagulation; and factor abnormalities. Data related to days of use, types of blood products administered, and worst levels of bilirubin, creatinine, and other biochemical parameters were collected. The data on medical complications occurring during the hospitalization included the date of presentation of acute myocardial infarction, pneumonia, pulmonary edema, disseminated intravascular coagulation, septic shock, diarrhea, and mucositis. The severity of these abnormalities were categorized as grade 0 to 5 AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events Criteria version 4,[6] corresponding a value of 0 to normal level and values of 1 to 5 to increasing levels of severity. When the worst level of clinical parameters was present on more than 1 day, preference was given to the date closest to the index date (Day −14 from death). We calculated the length of stay (LOS) in hospital and LOS in the ICU.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 15.0; SPSS, Inc). We reported frequencies, proportions, 95% confidence intervals (CIs) of proportions,[7] and measures of central tendency. We compared subgroups of patients and analyzed the association between continuous variables by using Student t tests, and when appropriate we used the Bonferroni correction. The associations between categorical and ordinal variables were analyzed using χ^2 tests. We reported the Fisher exact test when frequencies in a contingency table were < 6. All statistical analyses were conducted using IBM SPSS Statistics version 19 (SPSS Inc). For all analyses, significance was set at $P < .05$ (2-tailed).

Results

A total of 122 patients were included in the study. The demographic and clinical characteristics of the study group are shown in Table 1. Most of the patients (64, 52.5%) received intensive chemotherapy, 39 patients (32%) had therapy with a single agent, and 19 patients (15.6%) had a hypomethylating agent. No association was found between the number of therapeutic attempts and the type of salvage therapy.

Patients were admitted for the following reasons: febrile neutropenia 26 patients (21.3%), documented infections 31 patients (25.4%), dyspnea/hypoxemia 21 patients (17.2%), pain 17 patients (13.9%), or other reasons 24 patients (19.6%). Among patients with

Table 1 Demographic and Clinical Characteristics of Patients With Acute Myeloid Leukemia Who Received Salvage Therapy and Died in the Hospital During the Period of the Study

Characteristic	n (%)
Total	122 (100)
Age, Median (Range)	62 (19-88)
Men	65 (53.3)
Married	88 (72.7)
Length of Hospital Stay in Days, Median (Range)	12 (1-89)
Received Blood Products	121 (99.2)
Type of Salvage Therapy	
Single Agent, Investigational Phase I/II Clinical Trial	39 (32)
Hypomethylating Agent	19 (15.6)
Chemotherapy, Combination of Agents	64 (52.5)
Number of Attempts of Salvage Therapy, Median (Range)	3 (2-11)
Survival Since Last Attempt of Salvage Therapy in Days, Median (Range)	24 (1-155)
Admitted to Intensive Care Unit	97 (79.5)
Invasive Mechanical Ventilation	51 (41.8)
Dialysis	33 (27)
Two or More Vasopressors	43 (35.2)