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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

Background—Patients with acute myeloid leukemia (AML) and refractory disease receive investigational therapies within 2 months of their death. The attribution of serious adverse events (AE) in this phase to disease progression versus drug toxicity is tenuous. We aimed to determine the incidences of serious AE in the last two weeks of life of patients with refractory-relapse AML undergoing salvage therapy (ST).

Patients and Methods—Adults who received ST from September 2010 - December 2011 were evaluated. Data collected included incidences of serious AE, type of ST, medical complications, length of hospital stay and Intensive Care Unit stays, organ dysfunctions, and utilization of life support therapies.

Results—A total of 122 patients received ST. The majority (52%) received intensive chemotherapy; 32% had single drug investigational therapies, and 16% received therapy with hypomethylating agents. Common complications were pneumonia (82%), disseminated intravascular coagulopathy (59%) and septic shock (49%). Notable complications included: acute respiratory failure justifying invasive mechanical ventilation in 42%, renal failure requiring dialysis in 27%, atrial fibrillation in 30%, and prolonged prothrombin time (grade 3) in 56%. There was no difference in the incidence of these complications by type of ST.

Conclusions—Baseline expectations of serious AE 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 to 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.

Keywords

Acute myeloid leukemia; salvage therapy; adverse effects; drug toxicities

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INTRODUCTION

With modern intensive combination chemotherapy, patients with acute myeloid leukemia (AML) achieve complete remission rates of 50-80% and have long-term survival rates of 5 - 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 used³. Most patients relapse and require salvage therapies. Standard salvage therapies include cytarabine-based combinations but patients whose leukemia progresses on standard therapies often consider investigational therapies⁴. A critical component in evaluating the efficacy of investigational drugs is to determine the toxicities attributable to the new treatment versus complications anticipated from disease progression and from AML-associated cytopenias⁵. Knowledge of the expected incidences of these events can be used as a benchmark for baseline expectations against which the incidence of serious adverse events (AE) 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, in order 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 is to establish the baseline expectations of such serious AE 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 MD 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 two weeks before death in collecting data of serious AE, 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 utilization of life supportive infrastructures such as use of 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 was also recorded, as well as the date of last salvage therapy.

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: utilization of the Intensive Care Unit (ICU); invasive mechanical ventilation; need for dialysis; use of two or more vasopressors; abnormal chemistries, blood counts and coagulation; and factor abnormalities were also collected. Data related to days of utilization, 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 was categorized as grade 0 - 5 AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events Criteria version 4⁶, corresponding a value of 0 to normal level and values of 1 – 5 to increasing levels of severity. When the worst level of clinical parameters was present on more than one 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 as well as LOS in ICU.

Statistical analysis—Statistical analysis was performed using SPSS for Windows (version 15.0; SPSS, Inc., Chicago, IL). We reported frequencies, proportions, 95% confidence intervals (CI) of proportions⁷, and measures of central tendency. We compared subgroups of patients and analyzed the association between continuous variables by using Student's *t*-tests, when appropriate we used the Bonferroni correction. The associations between categorical and ordinal variables were analyzed by using chi-square tests. We reported the Fisher's exact test when frequencies in a contingency table were < 6. All statistical analyses were conducted using IBM SPSS Statistics version 19 (SPSS Inc., Chicago, Illinois, 2010). For all analyses, significance was set at $p < .05$ (two 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. The majority of the patients (52.5%) received intensive chemotherapy, 32% had therapy with a single agent, and 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 (21.3%), documented infections (25.4%), dyspnea/hypoxemia (17.2%), pain (13.9%), or other reasons (19.6%). Among patients with documented infections, the majority (58.1%) were diagnosed with pneumonia. A total of 79.5% were admitted to the ICU and 17.2% were transferred to the unit on the same day of admission to hospital. A large proportion of patients (41.8%) required mechanical ventilation; the median number of days under mechanical ventilation was 3.5 days. Nine (7.3%, 95% CI = 3% - 14%) patients had to be intubated and mechanically ventilated within the first 48 hours of hospital admission. Twenty-seven percent of the patients developed renal failure that justified dialysis; the median number of days on dialysis was 3; and only 6.5% (95% CI = 2% - 18%) received dialysis within the first 48 hours of hospital admission. We did not find differences in the numbers of LOS in

hospital (p-value = .35) or admission to ICU (p-value = .13), or utilization of mechanical ventilation (p-value = .14), dialysis (p-value = .76), or two or more vasopressors (p-value = .22) with the type of salvage therapy received.

Pneumonia (82%), disseminated intravascular coagulopathy (59%), and septic shock (49.2%) were the most frequent medical complications observed during the hospital stay. Among the patients with pneumonia, the proportions of patients who eventually developed septic shock or disseminated intravascular coagulopathy were 58% and 50%, respectively. Overall, 36.9% of patients had diarrhea, and 30.3% had atrial fibrillation. A total of 18% had infections other than pneumonia and 26.2% presented congestive heart failure or pulmonary edema. Acute myocardial infarction and mucositis were observed in 10.7% (95% CI = 6% - 17%) and 6.6% (95% CI = 3% - 12%) of the patients, respectively. Regardless of cardiovascular diseases, we found a large proportion of patients with atrial fibrillation and congestive heart failure were first diagnosed with these disorders after the index date, 67.6% and 75% respectively.

On the index date the majority of the patients (94.2%) had decreased platelet counts of grades 3 or 4 and when considering the worst level of thrombocytopenia observed during the period of study, the proportion increased to 99.2%. Oxygen saturation level < 88% was a rare event on Day - 14 before death (1.7%, 95% CI = 0 - 6%), but a large proportion of patients (49.6%) reached PaO₂ levels corresponding to grades 3 or 4 during the hospital stay. Although the majority (95.9%) of the patients had low albumin levels (grades 0 to 2) on Day - 14 before death, tests of hepatic function that eventually showed severe alterations during hospitalization were: aspartate transaminase (AST), alkaline phosphatase (ALP), alanine transferase (ALT), and total bilirubin levels (Table 2). The proportion of patients with total bilirubin of grades 3 - 4 was 21.3%. We observed 2 or more alterations of grades 3 - 4 on the tests of hepatic function in 18.8% of the patients. The incidence of prolonged prothrombin time of grade 3 was 55.7%.

Regarding renal function, in addition to patients who required dialysis, 3.2% (95% CI = 1% - 8%) reached high creatinine levels of grades 3 - 4. A similar proportion of patients 5.7% (95% CI = 0 - 15.7%) with the previous mentioned characteristics reached hyperkalemia of levels 3 - 4. No differences in the proportion of AE and toxicities were observed by the type of salvage therapy received (Table 2).

DISCUSSION

During the last two weeks of life, medical complications and serious AE were frequent among adults with AML who received salvage therapy; importantly, the level of severity of these events warranted admission to ICU in 79% of patients. Respiratory support with mechanical ventilation was required in 41.8% and dialysis in 27%. We also observed severe other organ dysfunctions including myocardial infarction in 10.7%, atrial fibrillation in 30.3%, severe liver dysfunction in 18.8%, and disseminated coagulopathy in 59%. Of interest, there were no significant associations between medical complications, serious AE, or utilization of services or procedures with the type of salvage therapy received (intensive chemotherapy versus investigational therapy versus hypomethylating agents).

In investigational Phase I-II trials, particular attention is paid to potential drug associated toxicities which can be serious and occurring at the higher level than acceptable⁸, for example in more than 20% of the patients. Because AML is associated with both, severe myelosuppression as well as leukemic proliferation disease and organ infiltrations, disease-related complications and not those attributable to treatment can often be the cause of deterioration and organ failure. This is important since excessive reporting of severe toxicities that are unrelated to the investigational drug may overburden the research infrastructure, distract from true drug related toxicities, and disregard effective investigational therapies because of erroneous attributions of side effects to the drug rather than the natural progression of AML. In particular we were surprised to see the high incidence of cardiac, pulmonary, hepatic, and renal complications in the terminal phase of AML. However, no differences in the proportions of complications, toxicities and AE were observed between the groups of patients evaluated.

Our study has important limitations, the use of data from a single institution, and lack of information on the patients who eventually died elsewhere. The use of data from a single institution limits the generalization of our findings due to variations in practice and patient population. Variation in medical practice affects the utilization of resources i.e. hospitalization or dialysis days; and patients who choose healthcare at our institution may be different than patients in other settings where clinical trials with investigational new agents are not available and/or patients are less inclined to participate in them. The lack of data from patients initially treated at our institution and who eventually died in other hospitals or at home could lead to underreporting of AE especially in the group of patients who preferred conventional chemotherapy. Indeed in this specific group of patients, the true magnitude of the risk of AE and toxicities could be higher than observed.

Phase I-II clinical trials are often designed to focus on the efficacy rather than on the safety of the new compounds with the aim to avoid false negative results. This means to falsely conclude that a new compound is ineffective leading to stop the progress of drug development and losing the potential benefit of the investigational compound⁹. Despite this fact and the limitations of our study, one would expect a higher incidence of toxicities and AE in the group of patients receiving investigational drugs nevertheless, no differences were found at the end-of-life of patients with AML receiving salvage therapies.

No studies have previously established this line of expectations of serious AE with salvage therapy in patients with AML. This study, although limited to the last two weeks of life, addresses this issue and can serve as a point of reference against which the incidence of complications of new treatments or regimens could be compared.

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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 ICU	97 (79.5)
Invasive mechanical ventilation	51 (41.8)
Dialysis	33 (27)
2 or more vasopressors	43 (35.2)

ICU, Intensive Care Unit

Severity of clinical parameters categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 by the type of salvage therapy received

Table 2

Clinical Parameters	All N (%)	Investigational N (%)	Hypomethylating N (%)	Chemotherapy N (%)	p-value
Total participants	122 (100)	39 (32)	19 (15.6)	64 (52.5)	NA
Decreased oxygenation (<88%) ^a	2 (1.7)	0	1 (5.3)	1 (1.6)	.35
Platelet count at index date ^a					.48
Grades 0 - 2	7 (5.7)	3 (7.7)	0	4 (6.3)	
Grades 3 - 4	115 (94.3)	36 (92.3)	19 (100)	60 (93.8)	
Hypoalbuminemia ^b					.84
Grades 0 - 2	117 (95.9)	38 (97.4)	18 (94.7)	61 (95.3)	
Grade 3	5 (4.1)	1 (2.6)	1 (5.3)	3 (4.7)	
Partial pressure of oxygen in arterial blood ^c					.16
Grade 0	55 (50.5)	21 (63.6)	6 (37.5)	28 (46.7)	
Grades 3 - 4	54 (49.5)	12 (36.4)	10 (62.5)	32 (53.3)	
Worst platelet count ^c					.34
Grades 0 - 2	1 (0.8)	1 (2.6)	0	0	
Grades 3 - 4	121 (99.2)	38 (97.4)	19 (100)	64 (100)	
Body temperature ^c					.63
< 38.0	33 (27.7)	10 (25.6)	7 (36.8)	16 (26.2)	
38.0	86 (72.3)	29 (74.4)	12 (63.2)	45 (73.8)	
AST ^c					.76
Grades 0 - 2	97 (82.2)	29 (78.4)	16 (84.2)	52 (83.9)	
Grades 3 - 4	21 (17.8)	8 (21.6)	3 (15.8)	10 (16.1)	
ALP ^c					.85
Grades 0 - 2	109 (90.1)	36 (92.3)	17 (89.5)	56 (88.9)	
Grade 3	12 (9.9)	3 (7.7)	2 (10.5)	7 (11.1)	

Clinical Parameters	All N (%)	Investigational N (%)	Hypomethylating N (%)	Chemotherapy N (%)	p-value
ALT ^c					.93
Grades 0 - 2	108 (88.5)	35 (89.7)	17 (89.5)	56 (87.5)	
Grades 3 - 4	14 (11.5)	4 (10.3)	2 (10.5)	8 (12.5)	
Total bilirubin ^c					.51
Grades 0 - 2	96 (78.7)	33 (84.6)	15 (78.9)	48 (75)	
Grades 3 - 4	26 (21.3)	6 (15.4)	4 (21.1)	16 (25)	
Creatinine ^c					.94
Grades 0 - 2	85 (69.7)	28 (71.8)	13 (68.4)	44 (68.8)	
Grades 3 - 4 or dialysis	37 (30.3)	11 (28.2)	6 (31.6)	20 (31.3)	
Prothrombin time ^c					.71
Grades 1 - 2	110 (90.2)	34 (87.2)	17 (89.5)	59 (92.2)	
Grade 3	12 (9.8)	5 (12.8)	2 (10.5)	5 (7.8)	
Hyperkalemia ^c					.13
Grades 0 - 2	113 (94.9)	33 (89.2)	18 (94.7)	62 (98.4)	
Grades 3 - 4	6 (5.1)	4 (10.8)	1 (5.3)	1 (1.6)	
Hypokalemia ^c					
Grades 0 - 1 or 2	81 (68.1)	27 (72.9)	11 (57.9)	43 (68.2)	.52
Grades 3 - 4	38 (31.9)	10 (27.1)	8 (42.1)	20 (31.7)	
Hypernatremia ^c					
Grades 0 - 2	36 (97.3)	18 (100)	57 (91.9)	111 (94.9)	.28
Grade 3	1 (2.7)	0	5 (8.1)	6 (5.1)	
Hyponatremia ^c					.21
Grades 0 - 1	29 (78.4)	17 (89.5)	57 (90.5)	103 (86.5)	
Grade 3	8 (21.6)	2 (10.5)	6 (9.5)	16 (13.4)	

Note: percentages may not add up to 100 due to rounding

NA, Not available; AST, aspartate transaminase; ALP, alkaline phosphatase; ALT, alanine transferase

^a14th day before death occurred

^b At hospital admission
^c Worst level observed during the period of study