# A Cohort Study of Patient-Reported Outcomes and Healthcare Utilization in Acute Myeloid Leukemia Patients Receiving Active Cancer Therapy in the Last Six Months of Life

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## Abstract

*Background:* Evidence about the unique palliative care needs of patients with acute myeloid leukemia (AML) is limited. Improving the care of these patients will require a better understanding of their unmet needs, including symptom burden at the end of life, and patterns of healthcare utilization.

*Objective:* To describe AML patients' experiences in the last six months of life regarding symptom burden, blood product utilization, and use of palliative care services.

*Methods:* Exploratory analysis of prospectively collected patient-reported outcomes and healthcare utilization data during the last six months of life among 33 AML patients who died during a longitudinal observational study.

*Results:* Symptom burden, quality of life (QOL), and psychological distress worsened with proximity to death. Of the 26 patients with utilization data, most ($n = 24$; 92.4%) were hospitalized in the last month of life, with 26.9% ($n = 7$) dying in the intensive care unit. Patients required a median of 16 red blood cell transfusions in the last six months of life, and those with a high transfusion burden in the last month of life had a higher rate of in-hospital death (blood transfusions: $p < 0.01$; platelet transfusions: $p = 0.03$). Only six patients enrolled in hospice (23.1%).

*Discussion:* Patients with AML have marked symptoms and QOL impairments that escalate in the final six months of life. Patients entering the healthcare system for active cancer treatment are likely to continue disease-oriented care until death. High rates of hospitalization and blood product transfusion are a direct barrier to transitioning to hospice care.

*Keywords:* acute myeloid leukemia; blood transfusion; palliative care; patient-reported outcomes; quality of life; symptom burden

## Introduction

PALLIATIVE CARE INTERVENTIONS improve patient-centered outcomes in advanced cancer.[1–3] However, much of this research has focused on patients with solid tumors and may not be generalizable to those with hematologic malignancies, who are less likely than solid tumor patients to receive consultative palliative care or enroll in hospice and more likely to receive disease-oriented end-of-life care or die in the hospital.[4–7] While a few studies evaluate the feasibility and impact of palliative care interventions on patients with hematologic malignancies,[8,9] relatively little is known about their unique palliative care needs. Moreover, the category of hematologic malignancy encompasses a multitude of disease entities and patient populations that require individualized study.

One such hematologic malignancy is acute myeloid leukemia (AML), which is a common, yet understudied, disease in palliative care. AML represents 30% of all new cases of leukemia annually in the United States, and results in about 10,000 deaths.[10] It is characterized by a poor prognosis, with only about 25% of adults living 5 years, and a median survival of just 8 to 10 months for those over age 59.[11] Developing effective palliative care interventions for AML patients requires an understanding of their unique needs.

Previous work suggests that AML patients have a high symptom burden[12,13] and many die in the hospital without accessing palliative care.[5,14] However, most studies have been cross-sectional, and the contributors to these outcomes remain unclear. Furthermore, specific measures of symptom burden and quality of life (QOL) are largely absent from this literature. In addition, use of blood transfusions has been identified by hematologists as a potential barrier to use of hospice care services, but this association has not been very well explored.[15]

To help address this knowledge gap, we analyzed data from a longitudinal study of AML patients' experiences while receiving chemotherapy at a major academic center (the setting in which most patients with AML are treated), who subsequently died. This exploratory analysis aimed to describe salient features about unmet needs among AML decedents during their last six months of life, with an emphasis on understudied features, including symptom burden, blood product utilization, and use of palliative care services. We hypothesized that patients receiving transfusion support would be less likely to utilize hospice care and more likely to die in the hospital.

## Methods

### Study design

The original study was a prospective, longitudinal study of QOL and symptom burden in patients with AML.[16] Eligible patients were adults with a diagnosis of AML, who were initiating chemotherapy at Duke Hospital. The Duke Institutional Review Board approved the study, and all subjects provided signed informed consent. Enrollment occurred from February 2014 to March 2015.

The study's patient-reported outcome (PRO) data from multiple time points are a unique and rich feature that enables this type of analysis. Of the 50 patients in the original study, 33 died before June 2016, the date of final chart review. Using these 33 decedents as the analysis cohort, we conducted an exploratory analysis and evaluated PRO data and healthcare utilization during the last six months of life for this small sample, and supplemented these data with manual chart reviews to assess utilization of healthcare services like transfusions and hospice.

### Assessments

Baseline assessments included demographics, performance status, and the presence of advance directives. Outcomes of interest included the following: QOL, symptoms, distress, number and duration of hospitalizations or intensive care unit (ICU) admissions, receipt of palliative care services (including hospice enrollment), blood product transfusions, and performance status (per the Karnofsky Performance Status [KPS] scale).[17] PROs were collected using personal computers or electronic tablets at baseline, weekly while hospitalized, and monthly in the outpatient setting. Symptoms were measured by the Patient Care Monitor (PCM) 2.0; QOL was measured by the Functional Assessment of Cancer Therapy Scale General (FACT-G), and the leukemia subscale (FACT-Leu); and distress was assessed by the National Comprehensive Cancer network (NCCN) distress thermometer (DT).

### Instruments

The PCM 2.0 is a symptom survey designed for use by practicing oncologists, which covers a full review of systems and supports both clinical decision-making and research purposes. It has been validated in multiple oncology populations and shares significant correlation with other instruments such as the FACT-G.[2,18–21] It comprises 86 items for women and 80 items for men, rated on 11-point (0–10) scales with higher scores indicating worse symptoms to a maximum score of 860 for women and 800 for men. The scale is divided such that 0 reflects no symptoms, 1 through 3 represent mild symptom burden, 4 through 6 represent moderate symptom burden, and 7 through 10 represent severe symptom burden. Items may be assessed individually, grouped into six subscales related to various domains of experience, or as a total score of symptom burden representing global QOL.

The FACT-G and FACT-Leu are QOL measures validated for oncology populations, with the latter specifically for patients with leukemia.[22,23] The FACT-G comprises 27 items grouped into four subscales, and the FACT-Leu adds a 17-item "leukemia subscale" to the FACT-G to comprise the total FACT-Leu instrument. All items are rated on 5-point (0–4) scales with higher total scores associated with better QOL. Previous studies using FACT-G demonstrate that changes of 5–7 points are clinically meaningful, out of a total maximum score of 108.[24] For the FACT-Leu total scale, changes of 13–17 points represent clinically significant differences, out of a total maximum score of 176.[22]

The NCCN DT is a single-item measure of self-reported psychological distress rated on an 11-point (0–10) scale with higher values indicating greater distress.[25] A trained research nurse determined the KPS score at each assessment point.

### Statistical analysis

We categorized follow-up time by the months preceding each subject's death, to facilitate this analysis, a method applied in other similar studies (thereby allowing the analysis to focus on the unmet palliative care needs of AML patients who died).[26,27] Follow-up periods were grouped into the last month of life (month 1); the second and third month leading up to death (months 2–3); and the fourth, fifth, and sixth month leading up to death (months 4–6). We calculated PCM total and subgroup scores, and FACT total and subgroup scores, according to standard methods. For each follow-up period, we represented each subjects' QOL and symptom burden using the average of survey results completed by each subject during that time period, to maximize data availability for each subject.

We calculated descriptive statistics for baseline and demographic data. We then calculated descriptive statistics of PCM, FACT questionnaires, DT scores, and healthcare utilization variables at baseline and at each follow-up period. We examined changes over time by applying the Wilcoxon rank-sum test to paired data, pairing month 1 with months 4–6 if available, or months 2–3 if not. Using the PCM data, we calculated the most frequently reported symptoms in the last 30 days of life.

Healthcare utilization variables included red blood cell (RBC) and platelet transfusions, with transfusion count defined as one unit of the specific blood product. We used Fisher's exact test to test the association between high transfusion burden in the last 30 days of life and the rate of having an in-hospital death, stratified by type of blood product (RBC vs. platelets). High transfusion burden was defined as >2 transfusions in the last 30 days, as per the schema used by Fletcher.[28]

TABLE 1. PATIENT BASELINE DATA

*Patient baseline data*

| | *Total (N = 33)* |
|---|---|
| **Age** | |
| Mean (SD) | 62.4 (9.8) |
| Median | 63.7 |
| Q1, Q3 | 57.2, 69.1 |
| Range | (36.4–79.7) |
| Age greater than 60 | 21 (63.6%) |
| **Gender, *n* (%)** | |
| Female | 15 (45.5) |
| Male | 18 (54.5) |
| **Race, *n* (%)** | |
| Caucasian/White | 28 (84.8) |
| Black/African American | 3 (9.1) |
| American Indian/Alaska Native | 1 (3.0) |
| More than one race | 1 (3.0) |
| **Charlson comorbidity index** | |
| Mean (SD) | 0.5 (1.4) |
| Median | 0.0 |
| Q1, Q3 | 0.0, 1.0 |
| Range | (0.0–7.0) |
| **KPS** | |
| Mean (SD) | 84.2 (12.3) |
| Median | 90.0 |
| Q1, Q3 | 80.0, 90.0 |
| Range | (60.0–100.0) |
| **Is this a newly diagnosed/first-line treatment set, *n* (%)** | |
| Newly diagnosed | 20 (60.6) |
| Relapse | 13 (39.4) |
| **Chromosomal karyotype at initial diagnosis, *n* (%)** | |
| Normal (46 XX or 46 XY) | 13 (39.4) |
| Complex (multiple abnormalities) | 20 (60.6) |
| Patient had at least one high-risk characteristic | 32 (97.0) |
| **Days from enrollment to death** | |
| Mean (SD) | 238.5 (184.5) |
| Median | 230.0 |
| Q1, Q3 | 69.0, 376.0 |
| Range | (12.0–617.0) |
| **Advance directive, *n* (%)** | |
| Not present | 28 (84.8) |
| Present | 5 (15.2) |

KPS, Karnofsky Performance Status.

If patients discontinued care at our site, we treated healthcare utilization data as missing for time periods after discontinuation. As such, if bias were introduced by nonrandom pattern of missing data, it would occur in the conservative direction (underestimating utilization outcomes like death in the hospital or transfusions).

**Results**

***Baseline characteristics***

Eighteen (54.5%) members of the cohort were male (Table 1). Subjects enrolled in the study at a median of 230 days before death. Most subjects (*n* = 20; 60.6%) had newly diagnosed AML,

TABLE 2. HEALTHCARE UTILIZATION DATA

*Healthcare utilization data*

| | *Total (N = 26)* |
|---|---|
| **Number of days hospitalized in last 30 days of life** | |
| N | 26 |
| Mean (SD) | 16.0 (10.6) |
| Median | 14.0 |
| Q1, Q3 | 6.0, 27.5 |
| Range | (1.0–30.0) |
| **Number of days in ICU in the last 30 days of life** | |
| N | 13 |
| Mean (SD) | 4.9 (5.7) |
| Median | 2.0 |
| Q1, Q3 | 1.0, 9.0 |
| Range | (1.0–18.0) |
| **Death in hospital** | 13 (50.0%) |
| Death in ICU | 7 (26.9%) |

ICU, intensive care unit.

and the remaining subjects were being treated for disease relapse. There were 32 (97%) high-risk patients, defined as age greater than 60 (*n* = 21; 63.6%), complex chromosomal karyotype (*n* = 20; 60.6%), or relapsed disease (*n* = 13; 39.4%). Twenty-six (78.8%) patients were initiating treatment with intensive induction chemotherapy (e.g., the ''7 + 3 regimen'' or similar), and the remainder was initiating palliative chemotherapy (e.g., low-dose chemotherapy such as with decitabine or azacitidine). Only five subjects (15.2%) had an advance directive on file at study enrollment.

***Quality of life, distress, and symptoms***

The total FACT-G median scores for paired data decreased 8.8 points, from 66.8 in earlier months to 58.0 in the last month of life ($p = 0.047$). FACT-Leu scores similarly decreased 17.5 points, from a median of 109.5 in earlier months to 92.0 in the last month ($p = 0.02$). DT median scores increased from 4.4 to 6.5 with proximity to death ($p = 0.08$). Median KPS scores also decreased over each time period.

Sixteen patients completed symptom surveys in the last month of life, and the symptoms that were most frequently reported as moderate to severe in the last month were fatigue (*n* = 9; 64.3%), inability to engage in hard work or activity (*n* = 8; 57.1%), and feeling anxious (*n* = 7; 50.0%). Other frequently reported moderate/severe symptoms included trouble sleeping (*n* = 6; 42.9%) and dry mouth (*n* = 6; 42.9%). Additional individual items are highlighted in Table 3. The median PCM total scores for paired data increased from 83.5 in earlier months to 154.8 in the last month of life ($p = 0.43$), indicating a nonstatistically significant increase in symptom burden with proximity to death.

***Healthcare utilization***

Of the 26 patients with available data who had documentation of receiving care at Duke in the last month of life, 24 (92.3%) were hospitalized (Table 2); patients spent a median of 14 days of their last month of life in the hospital (range 1–30). Thirteen (50.0%) were admitted to the ICU in the last month, and 7 (26.9%) died there. Of the 15 patients who had

TABLE 3. PHYSICAL SYMPTOMS MOST
FREQUENTLY REPORTED AS MODERATE/
SEVERE DURING LAST MONTH OF LIFE

| Physical symptom | Number of patients rating as moderate/severe (% of total N = 16) |
|---|---|
| Fatigue | 9 (64.3) |
| Trouble sleeping at night | 6 (42.9) |
| Dry mouth | 6 (42.9) |
| Change in the taste of food | 6 (42.9) |
| Easy bleeding | 6 (42.9) |
| Daytime sleepiness | 5 (35.7) |
| Physical pain | 5 (35.7) |
| Weight loss | 5 (35.7) |
| Diarrhea | 5 (35.7) |
| Swelling | 5 (35.7) |
| Weakness of body parts | 5 (35.7) |

an ICU admission at any point during the study, their median survival after the last ICU day was 3 days. Six patients (23.1%) were referred to palliative care, and this referral was made at a median of 39 days before death. Only six patients (23.1%) enrolled in hospice, with a median hospice length of stay of 8.5 days.

The RBC transfusion requirements, displayed in Table 4, were similar at each follow-up period. The median number of RBC transfusions given in the last six months of life was 16. The median platelet transfusion requirement increased from 1.0 in the four to six months before death to 5.0 in the last month. Patients with a high transfusion burden in the last month of life (for either RBC or platelet transfusions) had a significantly higher rate of in-hospital death (RBC transfusions: $p < 0.01$; platelet transfusions: $p = 0.03$).

## Discussion

This exploratory analysis provides a detailed account of AML patients' experiences in the last six months of life, and reveals three important findings: (1) this population has unmet symptom management and QOL needs that further increase with proximity to death, (2) under current treatment strategies, these patients have a large transfusion need that prohibits meaningful use of hospice care services, and (3) most patients continued disease-oriented care until death.

Our measures of symptom burden, distress, and QOL demonstrate a constellation of unmet palliative care needs, especially as patients approach death. In this small sample, a large percentage of AML patients faced moderate-to-severe fatigue, sleeplessness, and xerostomia. The high prevalence

of fatigue reported is consistent with recent work finding significantly higher rates of tiredness among patients with hematologic malignancy compared to patients with solid tumors.[29] The total FACT-G median scores indicate impaired QOL at all time points, with a median of 66.8 in the last four to six months of life. A study by Cella of a sample of patients with stage IV disease of varying solid malignancies found a mean FACT-G score of 80.1.[23] While the differences in that population make a direct comparison difficult to interpret, the lower scores in our sample may indicate a relatively larger negative impact of AML on QOL.

The decrements in QOL during the study period were also quite dramatic. The changes in total FACT-G and total FACT-Leu median scores, 8.8 and 17.5, respectively, were both clinically and statistically significant, even with only 10 pairs of available data. For the majority of remaining variables, the direction of the results was consistent. Similarly, the burden of psychological distress in patients with leukemia is known to be quite sizeable.[30–33] Our analysis demonstrating an increase in median DT scores adds to this literature, although the increase did not reach statistical significance. We suspect that this trend indeed reflects meaningful changes in distress, but that our sample size was underpowered to detect this.

Emerging evidence demonstrates the positive impact of early palliative care for patients with certain hematologic malignancies on the domains of physical symptoms and distress;[8] our findings emphasize the urgent need for further study of palliative care interventions in patients with AML. We are currently conducting a randomized trial of early, concurrent palliative care during intensive induction chemotherapy for patients with AML, to test the efficacy of upstream care at improving patients' experiences of illness (NCT02975869).

Transfusion burden in hematologic malignancies is often cited as a barrier to hospice utilization,[15] however, little evidence exists to support this assertion. We found a high transfusion need in AML patients in the last six months of life (median 16 U of RBCs), and we found a significant association between receipt of transfusions and rates of in-hospital death. This is consistent with the findings of Fletcher among patients with myelodysplastic syndromes, wherein transfusion dependent patients were more likely to die in the ICU and less likely to die in hospice.[28]

While we recognize that transfusion use may also relate to important clinical differences such as disease severity, transfusion needs represent a large obstacle to hospice enrollment for patients in the United States, the site of our study, wherein transfusion support is often not available to hospice enrollees. For example, in one national study, 40% of hospices surveyed reported refusing to provide any transfusion support.[34] Policy prescriptions are needed that reconsider

TABLE 4. BLOOD PRODUCT TRANSFUSION DATA

| Time period | Number of RBC transfusions | | | Number of platelet transfusions | | |
|---|---|---|---|---|---|---|
| | Mean (SD) | Median | Range | Mean (SD) | Median | Range |
| 6 Months to death (n = 23[a]) | 17.5 (12.13) | 16.0 | (0.0–48.0) | 18.0 (18.2) | 12.0 | (0.0–74.0) |
| 4–6 Months to death (n = 28[a]) | 5.4 (6.4) | 4.5 | (0.0–25.0) | 4.6 (7.2) | 1.0 | (0.0–27.0) |
| 2–3 Months to death (n = 29[a]) | 6.1 (5.7) | 5.0 | (0.0–17.0) | 6.4 (8.1) | 3.0 | (0.0–30.0) |
| 1 Month to death (n = 26[a]) | 6.4 (7.3) | 4.5 | (0.0–38.0) | 7.7 (7.7) | 5.0 | (0.0–26.0) |

[a]Sample size reflects number of patients for whom data were available at every time point in time range.
RBC, red blood cell.

transfusion offerings under the Medicare hospice benefit, and further research is needed into the role of symptom-based transfusion strategies to alleviate symptoms rather than to just treat laboratory numbers.[35]

Last, our results highlight a marked intensity of care at the end of life in patients with AML. A profound majority of those with available data, 92.3%, were hospitalized in the last 30 days of life. Half of those hospitalizations resulted in an ICU admission, and over a quarter of those hospitalized, died in the ICU. These high utilization rates and large percentage of patients dying in the hospital are consistent with other studies of older patients with AML.[5] A study by Cheng of elderly patients with AML referred to palliative care also found that roughly half of their study cohort died in the hospital.[36]

The high rates of hospitalization in our cohort are contrasted with the limited involvement of palliative care specialists, with only 23.1% of patients referred for consultation. This low proportion is consistent with the palliative care consultation rate of 16.2% seen for elderly patients with AML in another academic setting.[5] In addition, the finding that only a small minority of the cohort, 15.2%, had completed advance directives at the time of study enrollment is consistent with recent work by Freeman demonstrating similarly low rates of participation in advance care planning for patients with high-risk leukemia.[14]

Our sample of patients with AML seeking care at an academic center included a large proportion that continued receiving disease-oriented care until death, suggesting that this specific population is in need of earlier interventions to increase patient engagement in palliative care services and advance care planning.

The strength of this study lies in the depth of its data, which provide a more detailed look at individual patient experiences than existing large database studies. It also allows for longitudinal assessment of these factors, whereas most PRO-based studies in hematologic malignancies are only cross-sectional.

An important limitation is our small sample size and the exploratory nature of our analyses. The sample size precludes analysis of subgroups, such as between patients receiving intensive induction chemotherapy and more palliative, low-intensity chemotherapies, which likely represent distinctly different populations. Despite this, we found a statistical association with meaningful clinical implications for patient care. This study is a key first step with findings that should be further explored on a larger scale and in multiple settings.

Another limitation is the nonrandom pattern of missing data inherent in PRO-based work among patients near the end of life. The patients who were lost to follow-up may have elected for community-based hospice care, whereas those who maintained care at our institution may have self-selected for pursuing more intensive therapies. In addition, patients receiving AML treatment at an academic center may be different than those seen in the community.

It is also likely that some patients were too ill to complete surveys at certain points in their trajectory; this suggests that our findings may actually underrepresent the severity of unmet needs in this population, as those too ill to complete surveys are more likely to have greater needs and worse scores. In focusing on those patients who died during this longitudinal study, we were able to paint a vivid picture of the actual unmet needs of AML patients at end of life to inform subsequent interventions,

but readers should recognize the exploratory nature of this analysis.

In conclusion, patients with AML have unmet symptom needs and QOL impairments that escalate in the final six months of life, indicating a need for concurrent palliative care interventions earlier in the disease course. High rates of hospitalization and blood product transfusion are a direct barrier to hospice care and warrant changes in policy to better meet AML patients' needs. Further studies into the potential benefits of early palliative care intervention in patients with AML are warranted.

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## Author Disclosure Statement

No competing financial interests exist.

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