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The Impact of Remission Status on Patients' Experiences with Acute Myeloid Leukemia (AML): An Exploratory Analysis of Longitudinal Patient-Reported Outcomes Data

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Abstract

Purpose—Shared decision-making in acute myeloid leukemia (AML) requires understanding patients' longitudinal experiences of illness, but little is known about the impact of remission status on patient-reported outcomes (PROs). We aimed to explore the association between remission status and PROs 6-12 months following induction chemotherapy.

Methods—Forty-two patients completed three validated instruments characterizing symptom burden (Patient Care Monitor v2.0), distress (NCCN Distress Thermometer), and QOL (FACT-Leu), as part of a longitudinal observational study. We used regression models to explore the relationship between remission status and PROs, and explore differences by initial disease type (*de novo* versus secondary/relapsed AML).

Results—Those with secondary or relapsed AML at study onset had marked impairments in all measures compared to *de novo* AML patients. After 6 months, their mean distress score was 4.8 (4.0 warrants intervention), they reported a mean 14.1 moderate/severe symptoms, and had a mean QOL score of 113.6, compared to 1.0, 1.7, and 155.2, respectively, for those with *de novo* AML ($p < .0001$). Similarly, patients in relapse had a mean distress score of 5.3, a mean of 12.8 moderate/severe symptoms, and a mean QOL score of 113.4, compared to 1.8, 5.7, and 143.8, respectively, among those in remission ($p < 0.005$). These patterns persisted after adjusting for baseline differences ($p < .0001$).

Conclusion—Remission status is associated with markedly better patient well-being in AML. Patients with secondary or relapsed AML face severe symptom burden, distress, and QOL issues after induction. Interventions are needed to improve AML patients' experiences of illness.

Keywords

Acute myeloid leukemia; Quality of life; Distress; Symptom burden; Remission; Patient-reported outcomes

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. With about 21,000 new diagnoses each year in the U.S., over 10,000 die annually from the disease, and the overall 5-year survival rate is just 27% [1]. Yet prognosis and survival vary considerably by age, cytogenetics, and performance status. For example, older patients have higher morbidity and mortality, and those with genetic markers of high-risk disease have a 1-year survival rate of less than 10% [2]–[4]. On the other hand, younger patients, or those with favorable-risk markers, might be cured with standard treatments [5]. The juxtaposition of these outcomes and the uncertainty involved makes for a difficult and distressing decision-making scenario for many patients, as they have described to us in prior qualitative interviews [6], [7].

Initial decision-making in AML often centers on whether or not to receive intensive induction chemotherapy. Induction therapies confer the best chance at remission and prolonged survival, but are also associated with sizeable toxicity and risk. Patients receiving induction chemotherapy may face deconditioning, severe sepsis, invasive fungal infections, and treatment-induced cardiomyopathy, all of which pose a risk of early death, yet remission is not a guarantee. While much is known about clinical outcomes from induction therapy across various age groups and risk stratification schemas, much less is known about patients' actual lived experiences of these therapies. As such, an important data point is missing for patients who are approaching this decisional scenario. Some literature examines AML patients' experiences with induction chemotherapy by reporting overall quality of life (QOL) [8]–[14]. These studies, however, do not assess other important factors like distress and symptom burden, and most do not report QOL measures longitudinally beyond the first 3–4 months. In essence, the literature is missing important information about the patient experience that is essential for guiding treatment decision-making.

Our primary aim in this analysis is to explore the association between remission status and patient-reported outcomes (PROs) in patients with AML, and to further characterize QOL in the 6–12 month time frame following initiation of induction chemotherapy. We hypothesized that patients with relapsed or refractory disease may have worse PROs, along with those who did not achieve remission with induction chemotherapy. Identifying important differences in these measures will provide insight into how post-induction chemotherapy courses vary amongst AML patients, and highlight potential unmet needs in this population. Furthermore, an enhanced understanding of these issues can provide clinicians with important knowledge about their patients' post-induction courses that could influence clinical practice and decision-making, and facilitate the development and implementation of targeted interventions that address these shortcomings, including models of palliative care in hematology, an emerging area of research [15]–[21].

Materials and Methods

Study population

We enrolled adults with AML initiating a new line of inpatient chemotherapy at Duke University Hospital. Eligible subjects were English-speaking and either had newly-diagnosed or relapsed/refractory AML, without a prior stem cell transplantation for leukemia. Patients were enrolled consecutively from February 2014 through March 2015, and final data collection occurred in September 2015.

Ethics

The Institutional Review Board of the Duke University School of Medicine approved this protocol. Informed consent was obtained from all individual participants included in the study.

Study schema and data collection

We assessed PROs at enrollment, weekly during inpatient periods, and monthly during outpatient periods. Inpatients were able to complete the questionnaires on an electronic tablet, and outpatients used a secure website on their home computers. A backup paper option was offered to patients who were uncomfortable completing electronic surveys; none used this. Longitudinal data were collected for at least 6 months.

Measures

We measured patients' symptoms, distress, and QOL using three validated instruments: (1) the Patient Care Monitor, version 2.0 (PCM), (2) the Distress Thermometer (DT) tool from the National Comprehensive Cancer Network (NCCN), and (3) the Functional Assessment of Cancer Therapy Leukemia scale (FACT-Leu).

The PCM is an 80-item (86 in women) tool that provides a review of systems assessment in the oncology setting. Each item is rated on a 0 to 10 ordinal scale, with 10 being the most severe. On this scale, 0 reflects no symptom, 1-3 represents mild symptom burden, 4-6 represents moderate symptom burden, and 7-10 represents severe symptom burden. It includes 6 subscale domains: general physical symptoms, impaired ambulation, impaired performance, treatment side effects, distress, and despair, as well as additional unassigned symptoms not included in a calculable subscale. Our primary use of this scale is to report the number of moderate or severe symptoms experienced by patients [22]–[24].

The NCCN DT includes a single item to assess overall distress, rated on a 1 to 10 ordinal scale, and a 39-item "problem list" so patients can identify issues contributing to their distress. Correlations to existing screening tools for anxiety and depression (i.e. HADS and PHQ) suggest that this is a clinically useful screening tool for distress requiring intervention [25]. A DT score of 4 or above indicates clinically significant distress, warranting targeted attention. Many cancer centers are using this tool to inform routine outpatient care [26], [27].

The FACT-Leukemia instrument includes an oncology-specific overall QOL scale (FACT-G) and a leukemia-specific subscale. Together, these make up the FACT-Leu. FACT-G includes 27 items across four domains: physical, emotional, functional, and social well-being. The leukemia subscale includes 17 additional items specific to issues faced by patients with leukemias. Each item is rated on a 0 to 4 point ordinal scale, and then scored according to a published schema, available on facit.org. Higher scores indicate better QOL, and published data report clinically minimally interpretable differences for each scale and subscale [28], [29]. For example, for the FACT-G, changes of 5-7 points are clinically meaningful, out of a total maximum score of 108 [30]. For the FACT-Leu total scale score, changes of 13-17 points are clinically significant differences, out of a maximum score of 176 [28].

Statistical methods

We used descriptive statistics to assess baseline participant characteristics. We next examined the distribution of QOL, distress, and symptom burden from time of induction chemotherapy initiation. Data were grouped by the following assessment time points to facilitate longitudinal analyses: baseline, months 1, 2, 3-4, 5-6, and 7-12+.

We used nonparametric statistical tests to assess for differences in PROs between treatment groups at the 5-6 and 7-12+ month time points (unadjusted). We then grouped patients in two different ways to assess longitudinal differences in PROs, as per our *a priori* hypotheses. The first grouping was by initial disease status (*de novo* AML versus secondary/relapsed AML). We chose this grouping because people with secondary/relapsed AML tend to have poorer prognoses and therefore more challenging treatment courses than those with *de novo* AML. With this grouping, our aim was to measure the longitudinal trajectory of patient experiences based on initial disease status. The second grouping was by current disease status (remission versus relapse), whereby patients were actually re-categorized longitudinally as their disease status changed. We chose this grouping because the impact of relapsed disease on PROs has not yet been reported in the literature, yet is often presumed to be correlated. We then plotted mean PROs at each time point by these groups. Lastly, we used analysis of covariance (ANCOVA) to adjust for differences in baseline PRO measures and disease groups, to assess whether the same associations persisted after adjustment for potential confounders.

Results

Study characteristics

We enrolled 50 patients in the study. Seven of these patients were receiving a non-induction treatment regimen and were excluded from this analysis. One patient dropped out during baseline data collection and was thus excluded from the analysis dataset. Here we report on the 42 patients who received induction chemotherapy and were followed longitudinally.

Table 1 summarizes baseline characteristics. The mean age of participants was 59.2 years old. Forty-five percent of participants had an initial diagnosis of a *de novo* AML, and 55% had secondary or relapsed AML. We classified patients into three risk groups using the NCCN risk stratification guidelines for AML, which incorporate information on

chromosomal karyotype and additional markers like NPM1 or FLT3 mutation status; 61.9% of patients had adverse-risk AML [31]. Patients in each group did not have differing access to or utilization of palliative care, psychiatrists or psychologists, social work, or varying use of antidepressants.

Symptoms

As hypothesized, symptom burden varied by initial diagnosis (*de novo* versus secondary/relapsed AML) and also by current disease status (remission versus relapse). At 5-6 months, the mean number of reported moderate or severe symptoms on the PCM was 4.1 for those with *de novo* AML and 12.3 for those with a secondary/relapsed AML ($p = .0034$). These numbers were 1.7 and 14.1, respectively, at 7-12+ months ($p < .0001$). Symptom burden also varied by current disease status; the number of reported moderate or severe symptoms was 5.6 for those in remission at 5-6 months and 16.6 for those in relapse at that time ($p = .0001$). At 7-12+ months, these numbers were 5.7 and 12.8, respectively ($p = .0034$).

At both the 5-6 month and 7-12+ month time points, the three most commonly reported moderate or severe symptoms were: fatigue/tiredness (39.7%), difficulty with hard work/activity (39.7%), and difficulty running (29.8%). Additionally, at 5-6 months, 28.2% of patients reported moderate/severe trouble sleeping at night, and 26.8% reported difficulty functioning normally. At 7-12+ months, 25% of patients reported moderate/severe worry and also “weakness with body parts.”

Distress

Overall, patients reported marked distress at baseline via the DT, with a mean DT score of 4.4. This is above the threshold of 4 wherein intervention is recommended by the NCCN. For those with *de novo* AML, the DT score was 1.9 at 5-6 months and improved to 1.0 by 7-12+ months (Figure 1). For those with secondary/relapsed AML, DT scores were above the threshold of 4 at 5-6 months (4.1, $p = .0012$ compared to *de novo*) and 7-12+ months (4.8, $p < .0001$). For patients in remission, distress improved to 2.3 at 5-6 months and improved further to 1.8 by 7-12+ months (Figure 2). On the other hand, patients in relapse saw their lowest distress at 3-4 months, just below the threshold of 4. This worsened, then stabilized at 5.3 for 5-6 months ($p = .0008$, compared to remission) and 7-12+ months ($p < .0001$).

Quality of life

Patients with a diagnosis of *de novo* AML saw their lowest QOL during the first month, which corresponds to their hospitalization for treatment (Figure 3). From this low, QOL steadily improved, surpassing their baseline at 2 months and continuing to improve through 12 months, with a FACT-Leu score of 155.2 at 7-12+ months. For those with secondary/relapsed AML, QOL declined from their baseline to a low at 2 months. At 3-4 months it stabilized for the remainder of the follow-up, with a score of 113.6 at 7-12+ months ($p < .0001$ compared to *de novo*). Regardless of the initial diagnosis, patients reported similar QOL at the end of their hospitalization at 1 month. When examining QOL by disease status, patients in remission reported slightly lower than baseline QOL at the 1-month mark, and then QOL continued to improve throughout the remainder of follow-up, with a score of 143.8 at 7-12+ months (Figure 4). From baseline, those in relapse showed declining QOL

through 2 months, and had a score of 113.4 at 7-12+ months ($p=.0005$ compared to remission). Patients in relapse never achieved baseline QOL again.

Multivariable Model

Lastly, we fit an analysis of covariance (ANCOVA) model to adjust for differences in baseline PROs and disease groups to see if these associations remained (Table 2). In each case, there was a significant relationship between the outcome measure and disease group ($p < .0001$). Patients with an initial diagnosis of secondary/relapsed AML on average reported more moderate/severe symptoms, higher distress, and lower QOL, compared to patients with *de novo* AML. Similarly, compared to patients in remission at each time point, patients in relapse demonstrated the same pattern of declining and distressing PROs.

Discussion

This longitudinal patient-reported outcomes study provides an in-depth look into the natural history of patients' experiences receiving intensive chemotherapies for AML. To date, no other study has assessed symptom burden, distress, and QOL with the breadth and depth that our instruments afforded, at such a high assessment frequency (150 questions assessed weekly while inpatient and monthly otherwise). Most studies also do not provide this length of follow-up in PRO measures. Furthermore, little is known about PROs amongst patients in remission versus relapse, or those with *de novo* versus secondary/relapsed disease. Our study therefore represents the highest resolution look at AML patients' experiences with induction chemotherapy to date.

A few important findings warrant further discussion. First, the distress level seen in AML patients is extraordinary, and represents an unmet need. Distress is particularly significant amongst patients in relapse compared to those in remission. Patients in relapse experience clinically significant distress at all time points beyond a few months after induction. It is particularly concerning that there is a significant rise in their distress after 3-4 months. As such, patients in relapse several months after induction may need more attention to distress. Our results also demonstrate the same pattern of distress between initial disease status (*de novo* versus secondary/relapsed AML) and current disease status (relapse versus remission). With this information, early interventions aimed at alleviating distress, such as psychological interventions, or concurrent specialty palliative care, can be targeted to those with a diagnosis of secondary/relapsed AML, as they can be expected to experience significant distress throughout the course of their disease [17], [32], [33].

We also found that QOL is clearly associated with remission status. These findings support and expand upon literature looking at QOL in older adults with AML undergoing induction chemotherapy [11], [13] and patients in remission after induction therapy [12]. QOL issues several months after induction chemotherapy are severe for patients with relapsed disease. Even a year after beginning induction, these patients did not achieve baseline QOL. We observed this in both those in relapse at any given time point, and those with secondary/relapsed AML at the start of our study. These patients also experience high symptom burden during this time, which is important to consider when making treatment decisions [34]. Clinicians can use this information to direct early interventions aimed at alleviating these

issues in patients with secondary/relapsed disease, like exercise programs to alleviate fatigue, or specialist palliative and supportive care consultation to address symptoms, as they will have significant symptom burden and QOL issues throughout the course of their disease [35].

Lastly, we found that patients with secondary/relapsed AML face more severe distress and QOL issues longitudinally than those with *de novo* disease. Literature shows that clinical outcomes are worse in those with secondary or relapsed disease, and our study expands upon these findings by demonstrating that these patients' personal experiences are more difficult as well. Targeted interventions are needed in this population to improve patients' lived experiences of illness. We are currently conducting a randomized trial of concurrent specialist palliative care at initiation of induction chemotherapy in patients with high-risk disease, to test this hypothesis, given that concurrent specialist palliative care has been shown to improve symptoms, QOL, and other patient-centered outcomes among those undergoing intensive treatments like stem cell transplantation ([Clinicaltrials.gov NCT02975869](https://clinicaltrials.gov/ct2/show/study/NCT02975869)) [17].

While this study is unique in its depth and frequency of assessments, it has a few limitations. First, it is a single-site study at an academic center, with a small sample size. While most AML induction chemotherapy is given at academic centers, differences in care elsewhere could yield alternative results. An important next step is to replicate this work at multiple sites, in a larger sample. Second, all PROs were written in English, and reporting the experience of only an English-speaking population does not capture the experience of those who may predominantly speak other languages. Finally, as with any longitudinal PRO study, there may be issues of non-random missingness due to death or dropout, and also heterogeneity in what happens to patients over time (i.e. some relapse, some go on to transplant, some die, etc.) [36]. Since this was an exploratory analysis with a small sample size, we did not apply an imputation strategy, given concern that it would introduce more bias. Of note, when data are missing not at random in an ill population, the missing data is usually from the sickest participants [36]. In this situation, the bias is in the conservative direction, as the missing data will be of those with the most disease burden. Therefore, if anything, our results probably underestimate the severity of PRO scores in poor-prognosis groups. Recognizing these limitations, we approached the data in a way that highlights the unique strengths of our deep, longitudinal data. We therefore focused on how patient-reported symptom burden, distress, and quality of life changed over time, with a description of the specific symptoms that are most frequently reported. These findings warrant further testing in a larger, multisite setting, where additional methods for addressing missingness may be applied.

Conclusions

This exploratory analysis of PRO data provides an in-depth look into the symptom burden, distress levels, and QOL issues experienced by patients after receiving induction therapy for AML, and points to a significant relationship between PROs and remission status in the year after induction chemotherapy. This represents the highest resolution, longitudinal look at the AML patient experience after induction done to date. Our findings can be used to guide

treatment decision-making, inform patient care, and facilitate novel intervention development. We found that distress, symptom burden, and QOL impairments in the year following initiation of induction chemotherapy are significant and severe, especially in those diagnosed with a secondary/relapsed AML, or those who relapse at some point during the course of their disease. These findings illustrate marked unmet supportive care needs in this population. In addition, a diagnosis of secondary/relapsed AML can be used to identify patients early on who will be likely to face severe issues in the near term; interventions to improve patients' experiences should be targeted to this population in particular.

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Fig. 1.
Distress Thermometer Plot based on Initial Disease Status (bars represent 95% confidence intervals)

Fig. 2.
Distress Thermometer Plot based on Current Disease Status (bars represent 95% confidence intervals)

Fig. 3.
Overall QOL by FACT-Leu based on Initial Disease Status (bars represent 95% confidence intervals)

Fig. 4. Overall QOL by FACT-Leu based on Current Disease Status (bars represent 95% confidence intervals)

Table 1

Demographics by Initial Disease Status (N = 42)

	<i>de novo</i> AML (N=19)	Secondary/Relapsed AML (N=23)	Total (N=42)
Age			
Mean (SD)	62.1 (14.3)	56.8 (12.5)	59.2 (13.5)
Median	65.8	59.7	63.1
Q1, Q3	59.8, 70.2	51.2, 66.5	52.6, 67.8
Range	(31.5-80.6)	(24.5-73.3)	(24.5-80.6)
Female	9 (47.4%)	11 (47.8%)	20 (47.6%)
Marital Status			
Married	12 (63.2%)	17 (73.9%)	29 (69.0%)
Divorced	2 (10.5%)	3 (13.0%)	5 (11.9%)
Single	1 (5.3%)	3 (13.0%)	4 (9.5%)
Widowed	4 (21.1%)	0 (0.0%)	4 (9.5%)
Highest Level of Education Completed			
High School Diploma or equivalent	8 (42.1%)	6 (26.1%)	14 (33.3%)
Some College	3 (15.8%)	4 (17.4%)	7 (16.7%)
Vocational-Technical Degree	2 (10.5%)	1 (4.3%)	3 (7.1%)
Associate's Degree	1 (5.3%)	6 (26.1%)	7 (16.7%)
Bachelor's Degree	1 (5.3%)	3 (13.0%)	4 (9.5%)
Graduate Degree	4 (21.1%)	3 (13.0%)	7 (16.7%)
Race			
Caucasian/White)	18 (94.7%)	19 (82.6%)	37 (88.1%)
Black or African American	0 (0.0%)	2 (8.7%)	2 (4.8%)
American Indian/Alaska Native	0 (0.0%)	1 (4.3%)	1 (2.4%)
Asian	1 (5.3%)	0 (0.0%)	1 (2.4%)
More Than One Race	0 (0.0%)	1 (4.3%)	1 (2.4%)
Ethnicity			
Not Hispanic or Latino	19 (100.0%)	23 (100.0%)	42 (100.0%)
If relapsed, what is the number of prior treatment			
No Relapse	19 (100.0%)	13 (56.5%)	32 (76.2%)
1	0 (0.0%)	1 (4.3%)	1 (2.4%)
2	0 (0.0%)	5 (21.7%)	5 (11.9%)
3 or more	0 (0.0%)	4 (17.4%)	4 (9.5%)
Risk			
Favorable Risk	7 (36.8%)	1 (4.3%)	8 (19.0%)
Intermediate Risk	2 (10.5%)	6 (26.1%)	8 (19.0%)
Adverse Risk	10 (52.6%)	16 (69.6%)	26 (61.9%)

Table 2

Mean Difference in PROs

Mean Differences in PROs by Initial Diagnosis				
	<i>de novo</i> AML (N ₅₋₆ =35) (N ₇₋₁₂₊ =39)	AML (N ₅₋₆ =34) (N ₇₋₁₂₊ =39)	Total (N ₅₋₆ =69) (N ₇₋₁₂₊ =78)	ANCOVA
FACT-Leu Total Score				
(13-17 point difference is clinically meaningful)	147.2 (17.8)	113.7 (32.2)	130.0 (31.0)	<.0001
At 5-6 Months: Mean (SD)				
At 7-12+ Months: Mean (SD)	155.2 (13.0)	113.6 (31.6)	134.4 (31.8)	<.0001
Distress Thermometer (clinically significant if >4)				
At 5-6 Months: Mean (SD)	1.9 (1.9)	4.1 (2.9)	3.0 (2.7)	<.0001
At 7-12+ Months: Mean (SD)	1.0 (1.3)	4.8 (2.5)	2.9 (2.8)	<.0001
Number of reported Moderate/Severe Symptoms for PCM				
At 5-6 Months: Mean (SD)	4.1 (5.0)	12.3 (11.4)	8.1 (9.6)	<.0001
At 7-12+ Months: Mean (SD)	1.0 (1.3)	4.8 (2.5)	2.9 (2.8)	<.0001
Mean Differences in PROs by Current Disease Status				
	Relapse (N ₅₋₆ =16) (N ₇₋₁₂₊ =24)	Remission (N ₅₋₆ =53) (N ₇₋₁₂₊ =54)	Total (N ₅₋₆ =69) (N ₇₋₁₂₊ =78)	ANCOVA
FACT-Leu Total Score				
(13-17 point difference is clinically meaningful)	98.2 (30.9)	140.1 (23.5)	130.0 (31.0)	<.0001
At 5-6 Months: Mean (SD)				
At 7-12+ Months: Mean (SD)	113.4 (37.0)	143.8 (24.2)	134.4 (31.8)	<.0001
Distress Thermometer (clinically significant if >4)				
At 5-6 Months: Mean (SD)	5.3 (3.1)	2.3 (2.1)	3.0 (2.7)	<.0001
At 7-12+ Months: Mean (SD)	5.3 (2.7)	1.8 (2.0)	2.9 (2.8)	<.0001
Number of reported Moderate/Severe Symptoms for PCM				
At 5-6 Months: Mean (SD)	16.6 (11.2)	5.6 (7.5)	8.1 (9.6)	<.0001
At 7-12+ Months: Mean (SD)	12.8 (11.8)	5.7 (9.9)	7.9 (11.0)	<.0001