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ARTICLE

Acute myeloid leukemia

Quality of life and mood of older patients with acute myeloid leukemia (AML) receiving intensive and non-intensive chemotherapy

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Abstract

Older patients with AML face difficult treatment decisions as they can be treated either with 'intensive' chemotherapy requiring prolonged hospitalization, or 'non-intensive' chemotherapy. Although clinicians often perceive intensive chemotherapy as more burdensome, research is lacking on patients' quality of life (QOL) and psychological distress. We conducted a longitudinal study of older patients (≥60 years) newly diagnosed with AML receiving intensive (cytarabine/anthracycline combination) or non-intensive (hypomethylating agents) chemotherapy. We assessed patients' QOL [Functional-Assessment-of-Cancer-Therapy-Leukemia] and psychological distress [Hospital-Anxiety-and-Depression-Scale] at baseline and 2, 4, 8, 12, and 24 weeks after diagnosis. We enrolled 75.2% (100/133) of eligible patients within 72-hours of initiating intensive ($n = 50$) or non-intensive ($n = 50$) chemotherapy. Patient QOL improved over time ($\beta = 0.32$, $P = 0.013$). At baseline, 33.3% (33/100) and 30.0% (30/100) of patients reported clinically significant depression and anxiety symptoms, respectively, with no differences between groups. Patients' depression symptoms did not change over time, while their anxiety symptoms decreased over time ($\beta = -0.08$, $P < 0.001$). Patient-reported QOL, depression and anxiety symptoms did not differ significantly at any time point between those who received intensive versus non-intensive chemotherapy. Older patients with AML experience improvements in their QOL and anxiety while undergoing treatment. Patients receiving intensive and non-intensive chemotherapy have similar QOL and mood trajectories.

Introduction

Older adults (≥60 years of age) with acute myeloid leukemia (AML) have a relatively poor prognosis with a low chance for long-term disease-free survival [1, 2]. Currently, no consensus exists regarding the optimal initial treatment strategy for older patients with AML, especially those with comorbidities or poor performance status. Before the regulatory approval of several new agents for AML in 2017, treatment options included: (1) intensive chemotherapy using a combination of cytarabine and an anthracycline ('7 + 3' regimen, or equivalent), which requires a prolonged 4–6 week hospitalization [3, 4]; (2) non-intensive therapy with low-dose cytarabine or the hypomethylating agents decitabine or azacitidine, which can be often given in the outpatient setting [3, 5, 6]; (3) clinical trial enrollment [3]; or (4) supportive care alone without any disease-modifying therapy [3]. In academic settings, oncologists often recommend intensive therapy, which has a higher risk of morbidity and mortality, with the hope of attaining a complete remission to allow for potentially curative allogeneic hematopoietic stem cell transplantation for the medically fit patients versus non-intensive therapy or supportive care for patients who are older or frail [1, 7].

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Given the uncertainty regarding the optimal treatment strategy for older patients with AML, patients must consider the potential impact of their treatment choice on their overall quality of life (QOL) and mood [8]. In fact, in one study 97% of older patients with AML reported that their QOL is more important than length of life [9]. Unfortunately, research is lacking on the comparison of patients' experiences receiving intensive versus non-intensive therapy [10, 11]. In one study, investigators assessed the QOL and mood of older patients with leukemias but included only a small number of patients with AML [7], prohibiting any robust comparisons of the experience of patients receiving intensive and non-intensive chemotherapy [7]. Despite the limited data, there is a general acceptance by oncology clinicians that patients receiving intensive chemotherapy experience greater distress and poorer QOL compared to those receiving non-intensive therapy [7, 11, 12]. Nonetheless, studies are needed to test this assumption empirically by prospectively assessing and comparing the QOL and mood trajectories of older patients with AML receiving intensive and non-intensive chemotherapy.

The difficulties of AML and its treatment impact not only patients but also their caregivers (i.e., family members or friends). Caring for a loved one with cancer is challenging and requires significant physical and emotional stamina [13–15]. Caregivers often assume this role with little or no preparation and without the knowledge, resources, or skills to help them address the complex needs of patients with cancer [16–23]. Given this immense caregiving burden, studies are also needed to characterize the psychological distress that caregivers of older patients with AML experience.

The goal of this prospective, longitudinal study was to assess and compare over time the QOL, fatigue, and mood of older patients with AML receiving intensive and non-intensive chemotherapy. We also sought to examine the psychological distress experienced by caregivers of older patients with AML. Data from this study will not only inform the design of supportive care interventions to improve the experience of older patients with AML and their caregivers, but also help clarify the expected course of illness when receiving intensive versus non-intensive therapy so patients and their families can make optimal treatment decisions.

Methods

Participants

We recruited 100 patients ≥60 years with a new diagnosis of AML, including 50 initiating intensive therapy and 50 initiating non-intensive therapy. Intensive therapy was defined as '7 + 3' or a similar intensive chemotherapy regimen requiring 4–6-week hospitalization. Non-intensive therapy included hypomethylating agents, low-dose cytarabine, or other non-intensive chemotherapy treatments that do not require a prolonged hospitalization. Similar to other academic centers, oncologists at our institutions typically recommend intensive therapy for the medically fit patients and non-intensive therapy for those who are older or frail. Patients were required to be able to read questions in English or willing to complete questionnaires with the assistance of an interpreter. We excluded patients with significant uncontrolled psychiatric disorders, or other comorbid diseases such as dementia or severe cognitive impairment, which the oncologist believed prohibited their ability to complete the study procedures. As the goal of this study was to compare the QOL, fatigue, and mood of patients receiving intensive and non-intensive chemotherapy, we excluded patients receiving only supportive care (including those treated with hydroxyurea alone).

We asked enrolled patients to identify a caregiver (i.e., a relative or a friend) who could be invited to participate in the caregiver portion of this study. Caregivers were considered eligible if they were (1) an adult (≥18 years); and (2) a relative or a friend of the patient who either lived with the patient or had in person contact with him/her at least twice per week. Patients without a caregiver were still eligible to participate.

Study design and procedures

This prospective, longitudinal study of older patients with a new diagnosis of AML and their caregivers was approved by the Dana-Farber Harvard Cancer Center Institutional Review Board. We screened the inpatient leukemia census and the outpatient leukemia clinic schedules at two institutions in Boston to identify potentially eligible patients with a new diagnosis of AML between 07/01/2014 and 08/01/2016. Once a potentially eligible patient was identified, the research assistant (RA) then sought permission from the primary oncologist to approach the patient for study participation. After receiving permission, the RA approached eligible patients for study participation within 72 h of initiating intensive or non-intensive therapy. The RA reviewed the consent form with patients in a private setting and obtained written informed consent. Patients were required to complete baseline self-report assessments within 72 h of initiating therapy for AML. If the enrolled patient identified a caregiver, the RA offered the caregiver the opportunity to participate in the study either at the same time as the patient or within 72 h after the patient provided written informed consent. We had a separate consent form for caregivers, which similarly detailed the study procedures.

Study measures

Participants (patients and caregivers) completed study questionnaires at baseline within 72 h of initiating therapy

for AML (or for caregivers within 72 h of patient consent), week-2, week-4, week-8, week-12, and week-24 after enrollment (±1-week window). Participants not present in person in the hospital or clinic were able to complete study questionnaires over email using a secure link or telephone.

Patient-reported QOL and fatigue

We used the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leuk) to assess patients' QOL [24]. The FACT-Leuk consists of four subscales assessing physical, functional, emotional, and social wellbeing as well as additional questions specific to the leukemia population. Higher scores on the FAC-Leuk indicate better QOL. We measured patients' fatigue using the FACT-Fatigue subscale, which consists of 13-items regarding fatigue symptoms occurring within the past week. Lower scores indicate a greater fatigue burden [25, 26].

Patient and caregiver depression and anxiety symptoms

We measured participants' (patients and caregivers) anxiety and depression symptoms with the 14-item Hospital Anxiety and Depression Scale (HADS) [27]. The HADS consists of two subscales assessing anxiety and depression symptoms in the past week, with subscale scores ranging from 0 (no distress) to 21 (maximum distress) [27]. Patients also completed the Patient Health Questionnaire-9 (PHQ-9) to assess for major depressive syndrome. The PHQ-9 is a 9-item measure that evaluates symptoms of major depressive disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV [28]. Higher scores on the PHQ-9 indicate worse depression symptoms.

Demographic and clinical factors

Patients completed a demographic questionnaire that included age, gender, race, ethnicity, marital status, income, and educational level. Caregivers also reported their age, sex, race, ethnicity, religion, education, and relationship to the patient using fixed categories. We reviewed the electronic health records to obtain data on AML diagnosis, and cytogenetic and molecular profile. We used the European Leukemia Net risk stratification schema to classify disease risk [4, 29].

Statistical analysis

We performed statistical analyses using STATA (v9.3). We first calculated descriptive statistics, including means or medians for continuous variables depending on the normality of the data, and proportions for categorical variables. For all analyses, we considered 2-sided P-value < 0.05 to be statistically significant.

We computed linear mixed-effect models to characterize the trajectories of changes in patient-reported outcomes (FACT-Leuk, FACT-Fatigue, HADS-Depression, HADS-Anxiety, and PHQ-9) over time. Analyses estimated baseline values and rate of change separately for each outcome. We constructed each model in several steps. We first used a baseline model to estimate intercept and slope random effects for the outcome of interest. To compare patient-reported outcomes among those receiving intensive and non-intensive chemotherapy, we then added treatment strategy (intensive vs. non-intensive) as a fixed effect variable predicting both the outcome of interest and slope of change over time (treatment strategy X time interaction). We repeated all analyses adjusting for age and obtained similar results.

In addition to examining patients' depression and anxiety scores continuously, we also transformed the HADS scores into dichotomous outcomes reflecting the presence or absence of clinically significant depression and anxiety symptoms (HADS subscale > 7) at each time point [27]. We used a similar strategy to describe caregiver depression and anxiety symptoms over time.

Attrition and missing data

The missing data rate for patient-reported outcomes among those receiving intensive chemotherapy was 12%, 18%, 18%, 24%, and 36% at weeks 2, 4, 8, 12, and 24, respectively. The rate of missing data was higher among patients receiving non-intensive chemotherapy (week-2: 18%, week-4: 20%, week-8: 38%, week-12: 40%, and week-24: 56%). The majority of missing data (85%) were due to patient's health deterioration or death. To assess the impact of missing data on our mixed-effects model results, we used two-fold fully conditional multiple imputations to impute 10 complete datasets and aggregated model results obtained using the imputed datasets. Given the extent of missing data due to health deterioration or death (data not missing at random), we also utilized worst-case imputation method (worst possible outcome imputed for missing data) to compare QOL and mood among patients receiving intensive and non-intensive chemotherapy. For caregiver outcomes, we report available case analyses without any imputations given the low rate of missing data.

Sample size calculation

Assuming an attrition rate of 30%, with a sample size of 100, we had 84% power to detect a 7-point

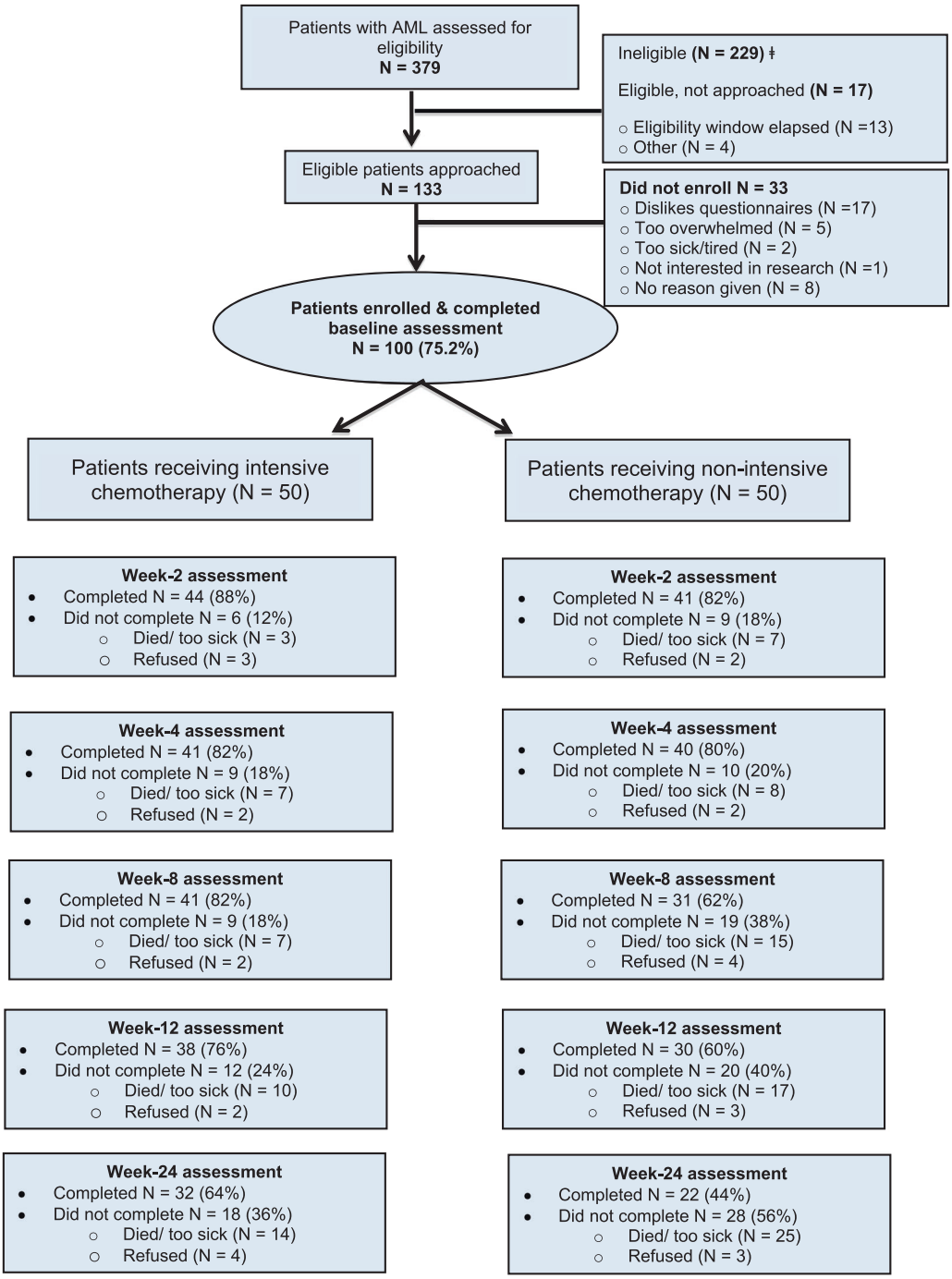

Fig. 1 Flow Diagram: AML = acute myeloid leukemia

difference in FACT-Leukemia scores between patients receiving intensive and non-intensive chemotherapy. A 7-point difference in the FACT-Leukemia score is considered clinically significant [24]. Thus, our study had adequate power to compare QOL trajectory between patients receiving intensive and non-intensive chemotherapy.

Results

Patient characteristics

We screened 379 patients with AML and identified 133 eligible patients for study participation (Fig. 1). We enrolled 75.2% (100/133) of potentially eligible patients

Table 1 Patient baseline characteristics

Characteristics	Intensive chemotherapy $n = 50$ (%)	Non-intensive chemotherapy $n = 50$ (%)	All participants ($n = 100$)
Age, median (range)	67 (60–83)	76 (63–100)	71 (60–100)
Female	20 (40%)	18 (36%)	38
Race			
White	47 (94%)	48 (96%)	92
African American	1 (2%)	0	1
Alaskan/ Native American	0	1 (2%)	1
Other	2 (4%)	1 (2%)	3
Hispanic ethnicity	5 (10%)	4 (8%)	9
Religion			
Catholic	14 (28%)	21 (42%)	35
Other Christian	19 (38%)	17 (34%)	36
Jewish	5 (10%)	6 (12%)	11
None	7 (14%)	6 (12%)	13
Missing	5 (10%)	0	5
Relationship status			
Married	40 (80%)	36 (72%)	76
Divorced	3 (6%)	3 (6%)	6
Single	3(6%)	2 (4%)	5
Widowed	1 (2%)	8 (16%)	9
Missing	3 (6%)	1 (2%)	4
Education			
Some high school	1 (2%)	2 (4%)	3
High school graduate	10 (20%)	10 (20%)	20
Some college	17 (34%)	12 (24%)	29
College graduate	9 (18%)	10 (20%)	19
Masters or Doctoral degree	10 (20%)	15 (30%)	25
Missing	3 (6%)	1 (2%)	4
Income			
<$25,000	3 (6%)	6 (12%)	9
$25,000 - $50,000	13 (26%)	13 (26%)	26
$51,000 - $100,000	16 (32%)	18 (36%)	34
>$100,000	11 (22%)	6 (12%)	17
Missing	7 (14%)	7 (14%)	14
Disease risk			
Low	3 (6%)	3 (6%)	6
Intermediate	23 (46%)	25 (50%)	48
High	24 (48%)	22 (44%)	46

Disease risk is classified based on the European Leukemia Net risk stratification

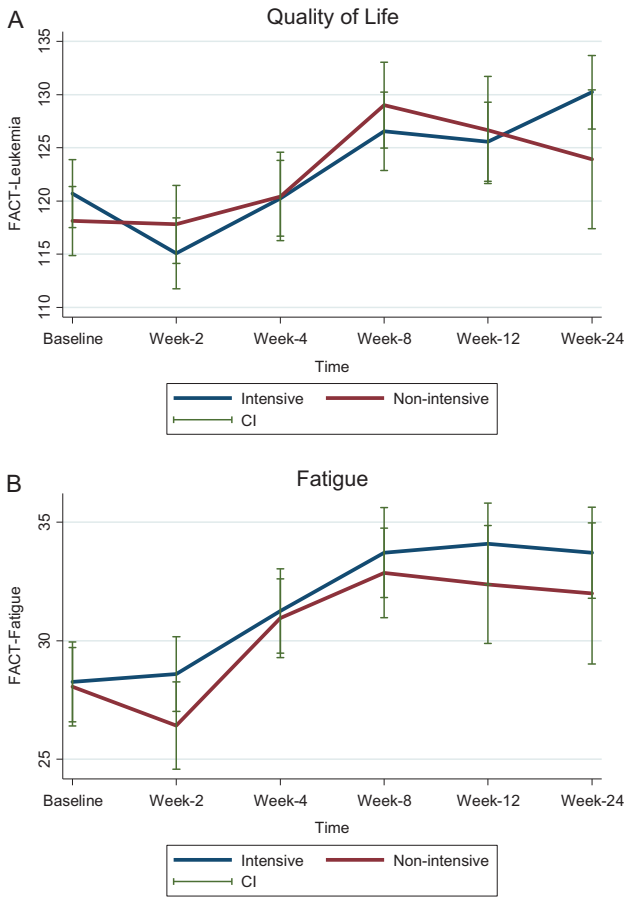

Fig. 2 Longitudinal patient QOL and fatigue. FACT = Functional Assessment of Cancer Therapy; QOL = quality of life; CI = 95% confidence interval. **a** Patient Quality of Life (FACT-Leukemia). **b** Patient Fatigue (FACT-Fatigue)

receiving intensive therapy ($n = 50$) or non-intensive therapy ($n = 50$). Table 1 depicts patients' baseline characteristics. Enrolled patients were mostly white (92%) with a median age of 71 years (range 60–100); and 38% were female. Participants receiving non-intensive chemotherapy were older (76 years vs. 67 years). No other baseline characteristics differed significantly between patients receiving intensive chemotherapy versus non-intensive chemotherapy.

Table 2 Comparison of longitudinal trends in patient-reported outcomes by treatment intensity

Variable	Baseline Mean	Week-2 Mean	Week-4 Mean	Week-8 Mean	Week-12 Mean	Week-24 Mean	Treatment intensity			Time X Treatment intensity		
							β	95%CI	*P*-value	*β*	95%CI	*P*-value
FACT-Leukemia							−1.22	−8.67, 6.23	0.748	−0.25	−0.75, 0.25	0.324
Intensive (ref)	120.69	115.08	120.24	126.54	125.56	130.23						
Non-intensive	118.12	117.81	120.42	129.00	126.67	123.91						
FACT-Fatigue							−0.99	−4.58, 2.60	0.588	−0.03	−0.29, 0.24	0.835
Intensive (ref)	28.27	28.59	31.26	33.71	34.09	33.71						
Non-intensive	28.06	26.43	30.95	32.86	32.37	32.00						
HADS-Depression							−0.64	−2.03, 0.76	0.371	0.07	−0.02, 0.15	0.119
Intensive (ref)	6.42	7.38	7.66	5.96	5.62	5.50						
Non-intensive	5.71	6.42	6.18	4.87	4.85	5.81						
HADS-Anxiety							0.11	−0.87, 1.09	0.826	−0.04	−0.12, 0.04	0.339
Intensive	5.37	3.92	4.00	3.63	3.84	3.44						
Non-intensive	5.66	5.06	4.61	3.04	3.89	3.36						
PHQ-9							−0.18	−1.81, 1.45	0.832	0.02	−0.10, 0.14	0.762
Intensive	7.04	7.75	8.08	5.95	5.34	5.5						
Non-intensive	7.24	8.16	6.51	4.75	5.31	5.81						

ref reference group, *FACT* Functional Assessment of Cancer Therapy, *HADS* Hospital Anxiety and Depression Scale, *PHQ-9* Patient Health Questionnaire-9, *β* beta estimate, *95%CI* 95% confidence interval

Patient QOL and fatigue

Figure 2 depicts longitudinal QOL and fatigue scores for patients receiving intensive and non-intensive chemotherapy. Patient QOL improved over time for the entire cohort ($\beta = 0.32$, 95%CI [0.07, 0.57], $P = 0.013$). When comparing patients receiving intensive and non-intensive chemotherapy, there were no significant differences in patient-reported QOL across all time points (treatment intensity $\beta = -1.22$, 95%CI [−8.67, 6.23], $P = 0.748$) or in slope of QOL change over time (treatment intensity X time $\beta = -0.25$, 95%CI [−0.75, 0.25], $P = 0.324$) (Table 2). Additionally, patient fatigue scores improved over time for the entire cohort ($\beta = 0.18$, 95%CI [0.05, 0.31], $P = 0.007$). As shown in Table 2, patients who received intensive versus non-intensive chemotherapy did not differ significantly in fatigue scores across all time points (treatment intensity $\beta = -0.99$, 95%CI [−4.58, 2.60], $P = 0.588$) or in slope of change in fatigue scores over time (treatment intensity X time $\beta = -0.03$, 95%CI [−0.29, 0.24], $P = 0.835$). Findings from multiple imputations (Supplemental Table 1) and worst-case imputations (data not shown) were similar for both patient-reported QOL and fatigue.

Patient depression and anxiety symptoms

Figure 3 depicts longitudinal depression and anxiety symptoms for patients receiving intensive and non-intensive chemotherapy. Patients' depression symptoms per the HADS did not change significantly over time ($\beta = -0.03$, 95%CI [−0.07, 0.01], $P = 0.132$), while their anxiety symptoms decreased over time ($\beta = -0.08$, 95%CI [−0.11, −0.04], $P < 0.001$). When comparing patients receiving intensive and non-intensive chemotherapy, there were no significant differences in patients' depression (HADS-Depression; PHQ-9) or anxiety (HADS-Anxiety) symptoms across all time points or in slope of change in these outcomes over time (Table 2). Findings were similar using multiple imputations (Supplemental Table 1) and worst-case imputations (data not shown). At baseline, a substantial minority of patients reported clinically significant depression (33%, 33/100) and anxiety (30%, 30/100) symptoms on the HADS (Fig. 4). The rates of clinically significant depression and anxiety symptoms did not differ between the two groups across all time points (Fig. 4).

Caregiver depression and anxiety symptoms

We enrolled 49 caregivers, as 26% of patients did not identify a caregiver for the study, and the remaining 25% of caregivers either refused to participate or were not available during the recruitment window to consent for study participation. The median age of enrolled caregivers was 67

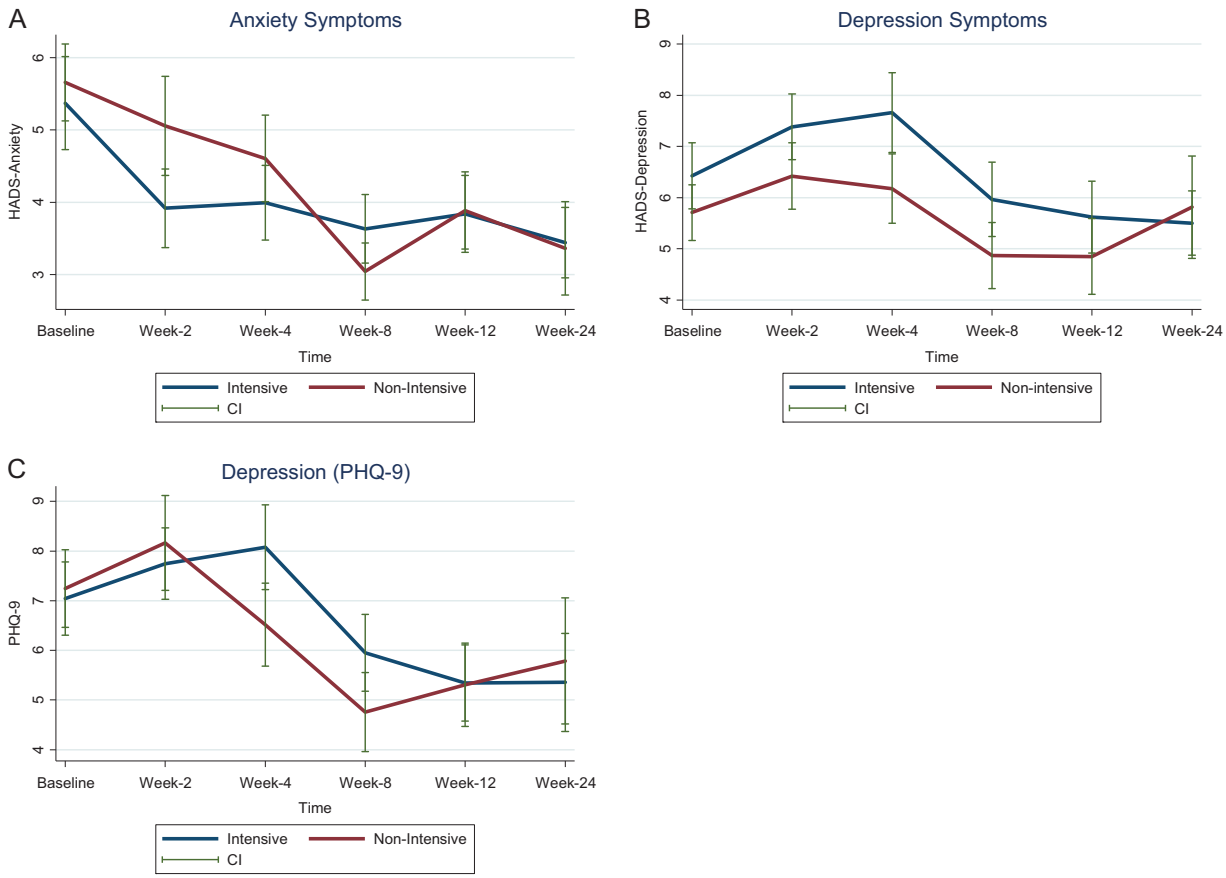

Fig. 3 Longitudinal Patient Depression and Anxiety Symptoms: HADS = Hospital Anxiety and Depression Scale; PHQ-9 = Patient Health Questionnaire-9; CI = 95% confidence interval. **a** Patient Anxiety symptoms (HADS-Anxiety). **b** Patient Depression symptoms (HADS-Depression); **c** Patient depression (PHQ-9)

(range 23–83), and 77.6% were female (38/49). The majority of caregivers were married to the patient (71.4%, 35/49) (Supplemental Table 2).

At baseline, 16.3% (8/49) and 44.9% (22/49) of caregivers reported clinically significant depression and anxiety symptoms, respectively (Fig. 5). Although caregiver depression symptoms did not change significantly over time ($\beta = -0.15$, 95%CI [−0.34, 0.03], $P = 0.102$), their anxiety symptoms decreased across study time points ($\beta = -0.23$, 95%CI [−0.45, −0.008], $P = 0.041$). Given that only 49 caregivers enrolled in the study, we did not compare caregivers' outcomes based on the patients' initial treatment strategy.

Discussion

In this prospective longitudinal study, we comprehensively examined the QOL and psychological burden of older patients with AML receiving intensive and non-intensive chemotherapy. Patients' QOL, fatigue, and anxiety symptoms improved over time, while their depression symptoms remained stable during the first six months after initiating therapy for their AML. This work also highlights the substantial psychological distress experienced by caregivers of older patients with AML, wherein nearly half of caregivers experiencing clinically significant anxiety symptoms at the time of their loved ones' diagnosis. Such data provide a clearer assessment of the experience of older patients with AML undergoing treatment and their caregivers, which should inform patients and families regarding their illness and treatment course in the future.

To our knowledge, this is the first robust study regarding the comparison of QOL and mood among patients receiving intensive and non-intensive chemotherapy [11]. Many oncology clinicians assume that patients receiving intensive chemotherapy endure greater impairments in QOL and psychological distress compared to those receiving non-intensive therapy, in part due to the prolonged treatment course and need for frequent hospitalizations [7, 8, 11, 12]. However, our findings suggest that patients receiving both intensive and non-intensive chemotherapy have similar QOL, fatigue, and mood trajectories during the first six months after therapy initiation. Importantly, these findings

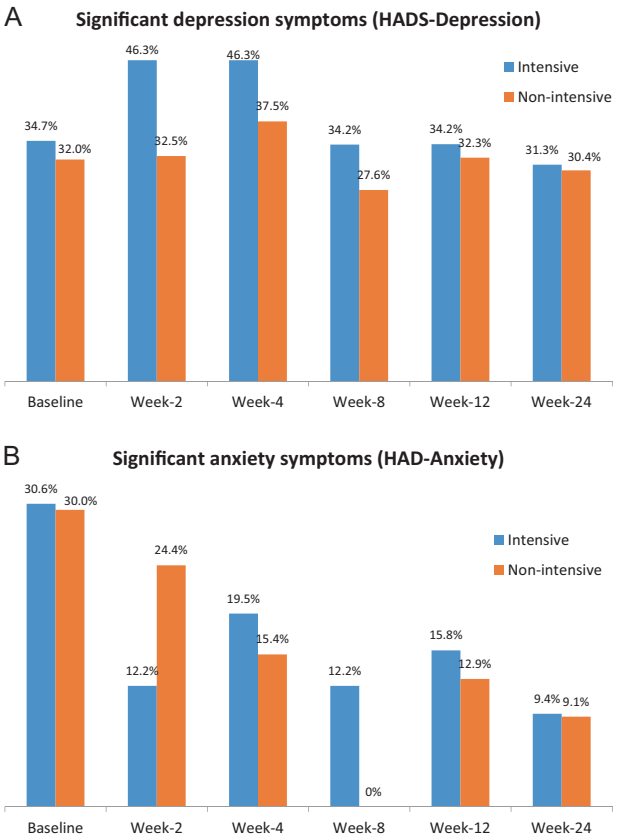

Fig. 4 Patients' clinically significant depression and anxiety symptoms. HAD-D = Hospital Anxiety and Depression Scale-Depression; HADS-A: Hospital Anxiety and Depression Scale-Anxiety. **a** Clinically significant depression symptoms. **b** Clinically significant anxiety symptoms

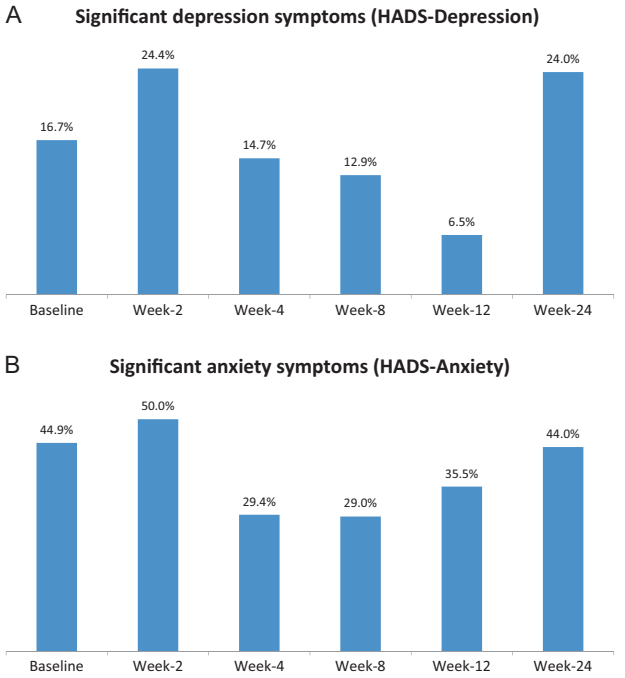

Fig. 5 Caregivers' clinically significant depression and anxiety symptoms. HAD-D = Hospital Anxiety and Depression Scale-Depression; HADS-A: Hospital Anxiety and Depression Scale-Anxiety. **a** Clinically significant depression symptoms. **b** Clinically significant anxiety symptoms

did not differ significantly when adjusting for age, using multiple imputations, or when imputing the worst possible patient-reported outcomes for missing data. The consistency of these findings across multiple imputation methods is particularly relevant given the known high rate of attrition in QOL studies of patients with AML due to health deterioration or death [11]. Notably, prior studies have demonstrated that older patients experience similar QOL and physical function to younger patients during and after intensive chemotherapy [30]. Thus, our findings provide useful data to better understand the QOL trajectory and psychological outcomes of patients receiving intensive and non-intensive chemotherapy that can be used to educate patients about their illness course.

We observed an improvement in QOL, fatigue, and anxiety symptoms during the first six months after initiating treatment for older patients with AML. These improvements in patient-reported outcomes are encouraging and should be used when discussing the potential benefits of initiating therapy in this population, regardless of the initial treatment strategy. Several prior studies have noted improvement in patient QOL, especially among those receiving intensive chemotherapy [7, 12, 26, 31]. Treatment response and the ability to achieve remission likely plays an important role in determining the extent of QOL improvement in this population [11, 32]. However, it is also important to note that over one-third of older patients with AML struggle with significant depression or anxiety symptoms throughout their illness course. Thus, supportive care interventions to reduce psychological distress in older patients with AML are clearly warranted, regardless of their initial treatment strategy.

To our knowledge, this is also the first study to explore the psychological burden experienced by caregivers of older patients with AML. Almost half of caregivers reported significant anxiety symptoms at the time of their loved ones' diagnosis, and close to a quarter struggled with depression symptoms during the course of illness. These rates of psychological distress are higher than the ones often seen in caregivers of patients with hematologic malignancies undergoing hematopoietic stem cell transplantation or those with solid tumors [15, 33–36]. Given the limited number of caregivers included in this investigation, we were unable to compare caregiver psychological distress based on the treatment strategy of the patient. Nonetheless, our data highlight the need to develop and test innovative supportive care interventions to address the caregiving burden and psychological distress in this vulnerable population.

Our study has several important limitations. First, the sample included mostly white, highly educated participants drawn from two urban tertiary care centers in the United States, and therefore these findings may not generalize to all older patients with AML and their caregivers. Our mostly white population included in this study reflects the demographics of our two hospitals and limits the generalizability of our findings. Second, this study was not a randomized clinical trial and thus there may be important biases affecting the QOL and psychological outcome data for patients receiving intensive and non-intensive chemotherapy. Third, although our study had lower rates of missing data compared to prior investigations [11], some data were still missing due to attrition, potentially biasing the results. We utilized multiple imputation strategies to ensure the fidelity and robustness of our findings, but no approach can entirely compensate for missing data. Fourth, given the limited sample size, we were unable to fully examine QOL and mood trajectories based on remission status among those receiving intensive versus non-intensive chemotherapy.

In sum, we demonstrated that older patients with newly diagnosed AML receiving therapy report improvement in their QOL, fatigue, and anxiety symptoms over time. This suggests a clear benefit to therapy for this population in terms of patient-reported outcomes. Importantly, the lived experience of older patients receiving intensive chemotherapy was similar to those receiving non-intensive therapy with respect to QOL, fatigue, and symptoms of depression and anxiety during the first six months after diagnosis. Strategies to enhance patients' understanding of their illness experience and their expected QOL trajectory may better inform their decision-making regarding the optimal treatment strategy for their disease. We have also demonstrated that both older patients with AML and their caregivers endure substantial psychological symptoms during the illness course, underscoring the need for psychological support to facilitate their effective coping.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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