Section Editors: Theresa Wicklin Gillespie and Constance Visovsky

ORIGINAL RESEARCH

Research Strategy for the Development of a Quality-of-Life Decision-Making Model for Older Patients With Acute Myeloid Leukemia

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2023.14.4.2

Abstract

Acute myeloid leukemia (AML) is a deadly cancer, especially for patients over 60 years of age who face the dilemma of choosing the best treatment during a time of crisis. Current research in the older AML population is focused on survival without addressing quality of life (QOL). Survival and QOL data are essential for patients to decide which treatment best aligns with their goals, whether for survival or improved QOL. **Research aims:** The aims of this study are to: (1) Describe differences in QOL among newly diagnosed older AML patients receiving intensive chemotherapy compared with nonintensive chemotherapy (at baseline, and days 30, 60, 90, and 180 post treatment); (2) Identify the individual clinical disease characteristics and patient factors of newly diagnosed AML patients that predict QOL among those receiving two treatment intensities; and (3) Design a patient decision-making model that integrates the significant clinical disease and patient factor predictors of QOL for newly diagnosed older AML patients. **Methods:** An exploratory observational design will be used to address aims 1 and 2. Data will be collected from 200 patients ≥ 60 years of age with newly diagnosed AML. Subjects will complete the Functional Assessment of Cancer Therapy-Leukemia, Brief Fatigue Inventory, and Memorial Symptom Assessment Short Form within 7 days of beginning new treatment and at days 30, 60, 90 and 180. Clinical disease characteristics will be completed by the health-care team. A patient decision-making model will be developed to provide survival and quality-of-life data for intensive and nonintensive chemotherapy.

J Adv Pract Oncol 2023;14(4):272–283

Prior to becoming a nurse and then nurse practitioner, I wanted to make an impact on the world by being a researcher. My career goals included a PhD. My desire to get married and start a family pushed that career goal down my life timeline to mid-career, after my children graduated from high school and no longer needed a doting mother. I began my PhD in 2010 while I worked full time as a nurse practitioner. I graduated in 2015 and grappled with the limitations of a 24-hour day. My research interest had been defined from several years of daily encounters with older acute myeloid leukemia (AML) patients who asked me questions that I could not answer, such as "How will these various treatments affect my quality of life?" and "What does this diagnosis mean for me and my family?"

My dissertation study included 86 older AML patients who were treated with intensive and nonintensive chemotherapy, and supportive care. I measured their quality of life twice, before treatment and at day 30, with the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) developed by David Cella, PhD, in 2012. Much to my surprise, patients who were treated with intensive chemotherapy had a statistically significant improvement in their quality of life (QOL) at day 30. This was shocking to me, and I reached out to the statistician on my dissertation committee because I was convinced that I analyzed the data incorrectly. Much to my bewilderment, I had analyzed the data correctly, and the intensive chemotherapy group fared better in terms of QOL compared with the nonintensive chemotherapy group. Another interesting finding was that the supportive care arm only had five women who chose not to pursue treatment because they did not want to burden their families. As you can imagine, I was captivated by this experience, which propelled me forward with an even fiercer desire to pursue research. However, I was not willing to abandon my clinical role.

This led to several meetings with various leaders at Moffitt Cancer Center. The role of a nurse practitioner researcher with independent research did not exist. Our program chair, Jeffrey Lancet, MD, advised me to create a business plan. In this article, you will find a portion of my business plan. I pursued a National Institutes of Health (NIH) K23 award, which provides for 75% protected time with a mentor. The goal of the K23 award is to develop skills as a researcher and provides protected time from a busy clinic schedule to develop into an independent researcher. In 2016, I took a grant writing class offered by Cecile A. Lengacher, RN, PhD, FAAN, FAPOS, at the University of South Florida. She is now my primary mentor. Her grant writing class and expertise as a researcher have resulted in NIH K23 funding, which was awarded during the throes of COVID-19. The research strategy detailed in this article is in progress.

To date, we have completed accrual of more than 200 patients, with equal numbers in the intensive and nonintensive chemotherapy arms. It has been challenging and stimulating to work toward providing patients with answers to their questions related to quality of life with different treatments. I hope that this provides inspiration and serves as an example of some of the requested information that is necessary for a K23 application. A portion of the score for a grant submission is based on the candidate, mentors, facility, and career development plan. I wish you the best in your research endeavors!

SIGNIFICANCE AND OVERALL SCIENTIFIC RIGOR OF PRIOR RESEARCH

Scientific Rigor of Research Concerning Treatment Decision-Making in AML

Acute myeloid leukemia is a bone marrow malignancy that occurs among older adults for whom optimal treatment is controversial due to inferior response rates and treatment-related toxicities (Tinsley et al., 2017). Acute myeloid leukemia is the most common form of adult acute leukemia, resulting in an estimated 21,450 new cases and 10,920 deaths in 2019 (Leach et al., 2006). The median age at diagnosis in the US is 68 years (LeBlanc & Abernethy, 2013). Treatment options for older AML patients are controversial and range from supportive care to hematopoietic stem cell transplant (Cogle, 2015; Miller et al., 2016).

For the first time since the 1970s, the treatment landscape is changing, and there is cautious optimism that survival will improve and toxicities will decrease, even in the older AML patient

(Ossenkoppele & Löwenberg, 2015). There have been seven new AML therapies approved since 2017 (Walter & Estey, 2015). This further complicates the decision-making process due to limited information on toxicities, QOL, and survival. Patients currently face a difficult decision in choosing the best treatment approach with a life-threatening blood cancer, as well as incomplete information regarding potential treatments. Under such circumstances, they may feel that QOL is an important factor in their decision; however, no scientifically rigorous model is available to enable shared decision-making between clinicians and patients to plan treatment that will be optimal for patients' QOL or survival. The impact of the problem is that patients may select expensive treatments that cause unnecessary suffering prior to death that do not align with their preferences, whether for life-prolonging treatment or optimal QOL.

Scientific Rigor of QOL Research Involving Older AML Patients

Research shows the unmet need for QOL research in older AML patients who have 5-year survival rates of < 10% (NCCN, 2016; Klepin et al., 2014; Siegel et al., 2019). Quality of life is a multidimensional concept that encompasses subjective aspects of life, including disease- and treatment-related symptoms and physical and psychological functioning (National Cancer Institute, 2018). Due to the personal nature of QOL, it is best measured with patient questionnaires that have been validated for measuring QOL. For this study, QOL would be measured using FACT-Leu, a 44-item, self-reported leukemia-specific measure (Juliusson et al., 2009). The FACT-Leu consists of 5 subscales: physical well-being, social well-being, emotional well-being, functional well-being, and leukemia-specific concerns. Often, QOL becomes the focus of treatment when cure is highly unlikely.

There is limited research examining QOL in AML. In a systematic review, 14 peer-reviewed studies focused on health-related QOL in patients diagnosed with AML from 2004 to 2014, although only three studies had a population with a mean age of 65 years or older (Kantarjian et al., 2010). Only two of the 14 studies were deemed robust because they used a leukemia-specific QOL instrument. This review demonstrated the negative impact of treatment on health-related QOL for patients in active treatment compared with survivors who were not in active treatment. Fatigue was the most troubling symptom, regardless of treatment. Four prospective studies that observed patients during and after AML chemotherapy (6–39 weeks post treatment) showed a rapid deterioration in health-related QOL shortly after diagnosis, followed by gradual improvement from weeks 2 to 6. One of the studies included patients who were receiving both intensive and nonintensive chemotherapy treatment. This review underscores the urgent need for robust QOL studies in older AML patients to inform decision-making by patients and their caregivers.

Scientific Rigor of Research Concerning Preferences and Goal-Congruent Care in Oncology

Individual values and preferences influence treatment decisions. Goal-congruent health care is care that is in alignment with patients' goals and value systems, and is culturally rooted (LeBlanc & Erba, 2019). To deliver goal-congruent health care, it is vital to provide patients and families with information on toxicities and anticipated benefits of treatment, along with information on QOL, thus aligning the AML treatment with their preferences. These discussions lead to better individualized treatment decisions for older AML patients (Click et al., 2018).

In a systematic review of 35 studies involving shared decision-making in oncology, barriers and facilitators were identified (Cannella et al., 2015). The primary barriers to shared decision-making were uncertainty in the treatment decision, apprehension regarding the side effects of treatment, and poor communication by the health-care provider. Facilitators included health-care provider consideration of patient preferences, positive physician actions, and encouragement of support systems. The focus is on the patient and health-care provider relationship, and communication skills to improve goal-congruent care. According to a study by Rood and colleagues (2017), shared decision-making was preferred by the majority of patients with hematologic malignancies (75%) and their caregivers (88%). Unfortunately, the information received was not sufficient in

order to participate in shared decision-making (Deschler et al., 2013). Additional research shows that the majority of patients with hematologic malignancies prefer to die at home; however, most die in hospitals (National Cancer Institute, 2020; Cella, 1994). In another study, older AML patients (84.5%) were hospitalized within 30 days of death, with only 16.2% of the patients receiving palliative care. Additional findings included underutilization of hospice services (23.1%). This reflects one of the criticisms of care provided for older patients with AML: poor quality of care and infrequent use of practices that are known to be effective (Cella et al., 2012). In contrast to solid tumor treatment, complications of AML are often acute unpredictable events, such as hemorrhagic or bleeding complications. This unpredictability underscores the critical need to elicit goals of care from patients early in the disease course to provide goal-congruent care should an acute event occur. Current research has not focused on individual disease characteristics and patient factors associated with optimal QOL; therefore, designing tailored therapy based on patient goals and shared decision-making has been suboptimal (Korol et al., 2017). There is a lack of evidence-based QOL guidance available to patients and their caregivers when choosing between treatments.

Scientific Rigor for QOL Predicted From Patient Factors

There is limited research on QOL predicted from patient factors in malignant hematology. A systematic review from phase II or III clinical trials in myelodysplastic syndromes (MDS) and AML evaluating symptoms and other health-related QOL concepts found 14 trials meeting the criteria. Fatigue was identified as the most distressing symptom for patients diagnosed with AML and high-risk MDS, which impairs QOL (Mead et al., 2013; Hack et al., 2005; Covvey et al., 2019). An analysis of age-related cytokine levels and cancer-related fatigue and QOL among AML patients found a small percentage of cancer-related fatigue and QOL was explained by cytokine levels (Rood et al., 2017). Quality-of-life symptoms were associated with significant improvements after treatment, including physical function, psychological distress, dyspnea, and positive effect (Howell et al., 2017). A cross-sectional correlation descriptive-analytical study (Howell et al., 2013) found associated factors with QOL and fatigue. Significant correlations of QOL in the Physical Component Summary were found with gender (p = .03) and marital status (p = .004). Results showed significant correlations between QOL in the Mental Component Summary with educational level (p = .01) and economic status (p = .02), and a significant correlation between fatigue and marital status (p = .005). Spearman correlation coefficients showed a significant correlation between fatigue with pain (p = .005). Also, statistically significant correlations were found between fatigue and economic status (p = .003).

Scientific Rigor for QOL Predicted From Significant Disease Characteristics

Current prognostic AML risk models incorporate disease characteristics to predict response to chemotherapy and survival but fail to incorporate QOL endpoints that are important to older AML patients (Institute of Medicine, 2013; Master et al., 2016). In a malignancy similar to AML, QOL research in myeloproliferative neoplasms (MPNS) has connected disease characteristics to symptoms. With MPNs, increased symptom burden has been correlated with advancing disease, specifically in polycythemia vera, indicating the need for specific therapy (ruxolitinib; Bryant et al., 2018). The link between QOL, disease characteristics, and treatment outcomes has been researched in gastric cancer, showing that a 15- to 20-point change in global QOL and functional scale scores predicted change in tumor status (Walter & Estey, 2015). By developing a model with incorporation of specific, significant disease characteristics in AML, patients and health-care providers will have a clearer picture of how disease characteristics affect the quality of survival.

Scientific Rigor for Patient Decision-Making Models

Shared decision-making models are advocated as the preferred approach to medical situations involving complex diagnoses and treatments when more than one reasonable medical treatment is available (Bryant et al., 2015). This helps to ensure

the alignment of treatment with patients' value systems. The two key ingredients identified in a systematic review were knowledge and power (Alibhai et al., 2020). The proposed research will provide knowledge to inform decision-making by patients and their support systems.

QOL in AML Logic Model

This theoretical model (Figure 1) postulates that QOL and survival are affected by individual patient factors and disease characteristics, including age, performance status, comorbidity, functional status, fatigue, symptoms, blast percentage, transfusion dependence, and cytogenetic risk group. Treatment decisions centered on survival are based on these individual disease characteristics and patient factors. Patients must decide how to handle their illness, guided by their health-care team. Patient preference for QOL or survival will be measured at baseline. Post-treatment QOL and survival will be modeled using disease characteristics and patient factors for each treatment intensity. By identifying significant variables that predict QOL and survival, a decision-making model can be developed to guide patients and health-care providers in selecting the intensity of therapy aligning with their goals, whether the preference is for survival or QOL, by providing probability of survival and probability of change in QOL score.

Significance for Training Nurse Researchers in QOL/Decision Models in AML

A systematic review of the 1945 to 2014 literature regarding the current and evidence-based roles of the nurse showed that nurses are integrally involved in the cancer decision-making process (Silverman et al., 2002). In the 33 articles reviewed, nurses were found to have complex roles in the decision-making process, depending on relationships, power, leadership, education, and experience, with a role in the multidisciplinary team to provide education and psychological support. Other nursing roles included symptom management and evaluation, as well as outcome evaluation. This evidence supports the nurse practitioner role as an ideal researcher in QOL decision models.

Summary

There is limited longitudinal research on QOL assisting older AML patients with decision-making based on clinical disease characteristics and patient factors. Aligning patient preferences with goals for end-of-life care is a major focus of the National Institute of Nursing Research, which is aimed at guiding future research directions in nursing science. Decision-making models are not available for older AML patients based on QOL data. Currently, only two studies have been

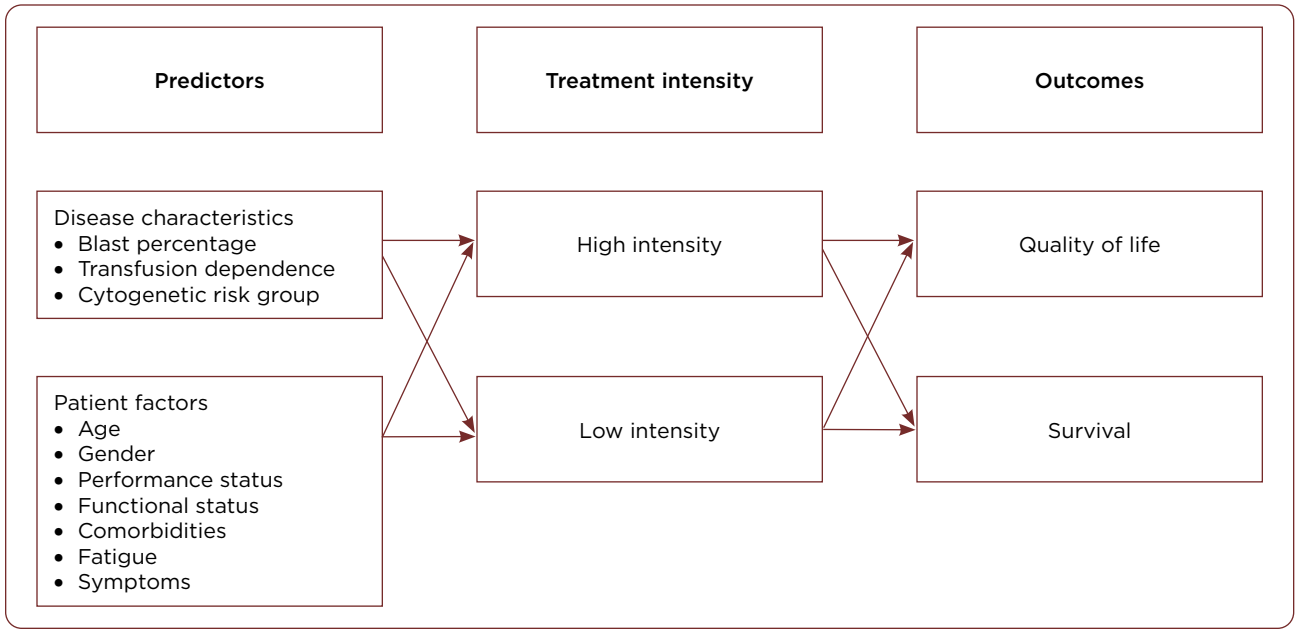

Figure 1. AML logic model.

identified on health-related QOL in AML patients (Kantarjian et al., 2010).

INNOVATION

The currently proposed research is highly innovative for the following reasons:

1. Individual disease characteristics and patient factors that predict QOL have not previously been identified among older AML patients.
2. Longitudinal evaluation of QOL in relation to treatment choices is not evident in older patients with AML.
3. This is the first study to develop a decision-making model based on QOL as an outcome for older patients diagnosed with AML based on significant disease characteristics and patient factors to predict QOL. If outcomes are achieved, this research may guide treatment decisions in older AML patients, aligning treatment with patient preference.

APPROACH

Overview

The National Comprehensive Cancer Network (NCCN) Guidelines for AML offer treatment recommendations based on age due to the inferior outcomes of patients ≥ 60 years of age treated with standard chemotherapy. Disease characteristics and patient factors are recommended for consideration in making treatment decisions, including performance status, adverse disease features, adverse cytogenetic risk group, and comorbidities. These recommendations are aimed at survival, and QOL is not included in the decision-making process (Musarezaie et al., 2014; Döhner et al., 2015).

Justification and Feasibility

Prior treatment decision-making models are based on predicting complete response rates and early death from intensive chemotherapy for patients ≥ 60 years of age diagnosed with AML (Mayer et al., 2014; Scherber et al., 2014). Factors incorporated into the models include age, comorbidities, performance status, cytogenetic risk group, and more recently, mutation analysis. Risk of early death from intensive chemotherapy has been reported with more advanced age, increased number and severity of comorbidities, and poor performance status (Scherber et al., 2014). Other disease-related factors for evaluating likelihood of remission include cytogenetic risk groups and mutation analysis. No decision-making model has incorporated QOL and considered treatment approach and predictors for a patient decision-making model.

Research Team and Setting

This application builds on the collaborative efforts of Moffitt Cancer Center and the University of South Florida. Dr. Tinsley will serve as the Principal Investigator (PI). The study's multidisciplinary team includes Drs. Sutton, Lengacher, Extermann, and Portman, who collectively have statistical, psychological, geriatric, and palliative care expertise in oncology clinical trials and translational behavioral research. These senior investigators have a strong track record of grant-funded research and clinical trials to support Dr. Tinsley. A research assistant will assist with patient recruitment, data collection, and entry into OnCore. Data from the cancer registry at Moffitt Cancer Center indicated a sufficient number of patients over 60 years of age with AML. There were 733 patients with AML in a 2-year timeframe. We estimate a completion rate of up to 100 participants yearly, thereby reaching the sample size goal within 2 years.

Preliminary Study

A pilot observational longitudinal design study among 85 high-risk MDS and AML patients (≥ 60 years of age) compared QOL between two treatment approaches before and 30 days following treatment. Results showed a mean age of 72 years with 94% being White males, and 79% (n = 67) completing the QOL measurements. Fatigue was a significant predictor of QOL ($p < .001$). Age and comorbidity were not significant predictors of QOL. Results were limited by a small sample size, age range, and underrepresentation of female patients (n = 29). Additional results showed a group-by-time interaction ($F = 4.56$, $p = .040$), with individuals treated with intensive chemotherapy showing a significant improvement in their QOL scores after treatment. Our application extends the work of this pilot study in a more scientifically rigorous and larger study with multiple QOL measures and outcomes post treatment to develop a decision-making model.

Research Design

Using an exploratory observational design to address aims 1 and 2, data will be collected from 200 patients 60 years of age or older with newly diagnosed AML. This will be measured at similar timepoints in their treatments: within 7 days of beginning new treatment and at days 30, 60, 90, and 180. It is expected that approximately 120 out of 200 patients will receive high-intensity treatment for their disease.

Methods (Specific Aims 1, 2, and 3)

Setting and Subjects. A total of 200 participants (150 expected to complete the study) will be recruited from the Malignant Hematology Department and Senior Adult Oncology Division at Moffitt Cancer Center in Tampa, Florida. There are adequate numbers of potential patients, with more than 400 new leukemia patients seen annually. A previous study of 85 patients in a short time frame without a research assistant confirms study feasibility (Covvey et al., 2019). Recruitment is anticipated to be completed in 2 years, and QOL measurements are anticipated to be completed in 2.5 years.

Inclusion Criteria. All patients ≥ 60 years of age newly diagnosed with pathology-confirmed diagnoses of AML who are within 7 days of starting a new treatment will be included. Subjects must be able to read and speak English at the eighth-grade level.

Exclusion Criteria. Patients < 60 years of age, and patients with another malignancy, dementia, traumatic brain injury, or individuals with central nervous system involvement of their leukemia will be excluded from the study. Cognitive status will be assessed by orientation to person, place, and time.

Randomization. Randomization is not possible due to the nature of the illness.

A research assistant will collect all data during clinic visits when possible. Pen and paper will be used for administering questionnaires at all timepoints. A script for reviewing preference will be used for consistently discussing survival vs. quality of life with each patient. Questionnaires will be answered by the patient, with a research assistant available to answer any questions. Data will then be transferred to an Excel spreadsheet.

Measurements for Predictors and Outcome Variables

Factors will include age, gender, performance status, functional status, comorbidity, fatigue, symptoms, blast percentage, transfusion dependence, and cytogenetic risk group based on leukemia research focused on survival (Korol et al., 2017). Factors will be measured at baseline. Performance status will be measured using Eastern Cooperative Oncology Group performance status. Comorbidity will be measured using the hematopoietic cell transplantation–specific comorbidity index (Stiggelbout et al., 2015; Joseph-Williams et al., 2014). Functional status will be measured using the Clinical Frailty Scale (Tariman & Szubski, 2015). The Brief Fatigue Inventory will assess fatigue at the time of enrollment (NCCN, 2018). For transfusion dependence, the number and frequency of transfusions with packed red blood cells will be captured for the 8-week period prior to signing informed consent. Cytogenetic risk group will be designated according to the guidelines for AML, as defined in the NCCN Guidelines for risk assessment (2019). The short form for the Memorial Symptom Assessment Scale will be used to measure the symptoms experienced by patients (Krug et al., 2010). This will be administered at study enrollment. The outcome variable is QOL and will be measured using the FACT-Leu (Juliusson et al., 2009). This well-validated and reliable instrument captures the symptoms unique to patients diagnosed with AML. See Table 1 for psychometric properties and timepoints for measurement.

Recruitment, Data Collection, and Procedures

Recruitment and Screening. Dr. Tinsley has collaborative relationships with the staff who will assist in identifying individuals who qualify for the study. Patients who are eligible for the study and express an interest will be contacted for further discussion and review of the informed consent with the research assistant. This will occur in the clinic setting.

Data Collection Procedures. Data collection intervals will include a baseline data collection including age, performance status, functional status, comorbidity, fatigue, symptoms, blast percentage, transfusion dependence, and cytogenetic

Table 1. Instruments With Psychometric Properties and Measurement Timepoints

Instrument and timepoints	No. of items	Domains measured	Scale	Recall period	Inclusion of AML patients in sample	Reliability	Validity
Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) Baseline, 30 d, 60 d, 90 d, and 180 d	44	Physical well-being, social/family well-being, emotional well-being, functional well-being, leukemia subscale	0–4 Likert, 0 = not at all, 4 = very much	Past 7 days	27/79 (34%) with acute leukemia	17-item Leu subscale score with internal consistency; α = 0.86 (T1), 0.88 (T2), and 0.87 (T3). Test-retest reliability for subscales with intra class correlations range from 0.765–089	Convergent validity Spearman correlation coefficients ranged from 0.28 to 0.64, compared to Medical Research Council of EORTC Leukemia Questionnaire
Memorial Symptom Assessment Short Form Baseline, 30 d, 60 d, 90 d, and 180 d	32	Global distress index, physical symptoms distress score, psychological distress score	Global and physical symptoms scored 0–4 from "no symptom" to "very much." Distress rated on a 5-point Likert scale (0-4), not at all to very much. Psychological symptoms scored as rarely (1), occasionally (2), frequently (3), and almost constantly (4)	Past 7 days	120/299 (40%) of patients with hematologic malignancies	Cronbach's alpha coefficient: Global distress index 0.80, Physical symptom distress 0.82, Total symptom distress 0.87	Criterion validity with FACT-G: Correlation coefficients with Physical symptom distress r = –0.74 (p < .001), Psychological symptoms r = –0.68 (p < .001), Global distress index r = 0.70 (p < .001)
Brief Fatigue Inventory Baseline, 30 d, 60 d, 90 d, and 180 d	9	Fatigue	Items rated 0–10. Three items ask patients to rate severity of their fatigue at its "worst," "usual," and "now" during waking hours, 0 = "no fatigue" and 10 = "fatigue as bad as imaginable." Six items assess fatigue that interfered with different aspects of patient's life during past 24 hours	Past 24 hours	51/305 (17%) patients	Cronbach's alpha coefficient: 0.96	Concurrent validity with FACT-G: r = –0.88 (p < .001); Profile of Mood States (POMS); r = 0.84 (p < .001)
Clinical Frailty Scale Baseline	7	Frailty	1 = Very fit; 2 = Well; 3 = Well, with treated comorbid conditions; 4 = Apparently vulnerable; 5 = Mildly frail; 6 = Moderately frail; 7 = Severely frail	Time of evaluation	Not provided	Intra class correlation coefficient: 0.97 (p < .001)	Concurrent validity with mathematically derived frailty index Pearson coefficient of 0.80 (p < .01)
HCT-CI Baseline	17	Comorbidities	0 = Low; 1-2 = Intermediate; ≥ 3 = High	Time of transplant	290/1055 (27%)	Inter-rater reliability of between 0.89 and 0.97	Predictive c-value of 0.69 for predicting non-relapse mortality

Note. EORTC = European Organization for Research and Treatment of Cancer; HCT-CI = hematopoietic cell transplantation–specific comorbidity index.

risk group after informed consent signed. There will be an attempt to match male participants within each treatment group with female participants to equally represent both sexes. Quality of life data will be collected at baseline, 30 days, 60 days, 90 days, and 180 days (Table 1). Patient preference, whether for survival at all costs vs. quality of life, even with shorter survival, will be measured prior to the treatment decision and again at 180 days to evaluate whether treatment aligns with patient preference.

Intensive chemotherapy is defined as any induction chemotherapy that is administered inpatient with a minimum of a 3-week hospitalization. Nonintensive chemotherapy includes outpatient treatments, predominantly hypomethylating agents, but also oral chemotherapy.

Data Analyses

For Aim 1, to describe QOL following two treatment approaches among newly diagnosed AML patients who are ≥ 60 years of age, average QOL measures for intensive vs. nonintensive treatment will be compared at each follow-up assessment (e.g., 30 days) using linear regression. Patient and disease characteristics that differ by treatment group will be included in the model as potential confounding factors, with the focus on treatment group differences. Quantitative data will be collected using the FACT-Leu.

For Aim 2, to identify individual baseline disease characteristics and patient factors among newly diagnosed older (≥ 60 years of age) AML patients that can predict changes in QOL for each of the two treatment approaches, based on longitudinal quantitative data, the following factors will be examined: age, performance status, functional status, comorbidity, fatigue, non-fatigue symptoms, blast percentage, transfusion dependence, and cytogenetic risk group. To achieve Aim 2, a correlative observational study will be performed to identify individual factors, including age, performance status, functional status, comorbidity, fatigue, symptoms, blast percentage, transfusion dependence, and cytogenetic risk group as predictors of changes in QOL within intensive and nonintensive chemotherapy treatment. Primary analyses will use data only from those who complete the surveys at each timepoint. Supplemental analyses will be used following management of missing data techniques, if necessitated by excessive missing data among survivors. The goal is to identify variables that can be used in the QOL component of the decision-making model to be created in aim 3.

Aim 3 is to design a decision-making model that incorporates QOL measures based on the results of aims 1 and 2. A Markov microsimulation model will be created using TreeAge Pro, including the variables identified in aims 1 and 2 as influencing QOL. We will elicit QOL utilities for various Markov states based on the results of the FACT-Leu scores and concomitant AML status-living situations. We will explore the sensitivity and stability of the model preferences for different values of QOL utilities. Using the model, we will assess (A) the QOL benefits of intensive vs. nonintensive chemotherapy treatment for patients with different baseline conditions for disease and patient parameters, and (B) the impact of patient trade-offs between QOL and survival on treatment preferences, given each baseline condition. This approach will allow both the estimate of group statistics and individualization of preferences for shared decision-making in future projects.

Power Analyses

Based on logistic and practical considerations, the target sample size is 200 patients. Of those, 120 are expected to receive intensive treatment. In short, this target sample size is sufficient to detect treatment-group differences and within-group correlations that are at least medium sized. For aim 1, to evaluate differences in QOL for those receiving intensive vs. nonintensive chemotherapy, the initial sample size is expected to decrease over time by 5% at 30 days, 10% at 60 days, 20% at 90 days, and 30% at 180 days. With $\alpha = .05$ for a two-sided test, power is at least .80 to detect the equivalent of Cohen's $d = 0.42$, a small to medium effect size at 30 days, and $d = 0.50$, a medium effect size at 180 days. For aim 2, to identify the clinical disease characteristics and patient factors that predict QOL among those receiving intensive or nonintensive chemotherapy, statistical power will vary by treatment group and follow-up assessment (decreasing over time). The analyses with the most statistical power will be for the intensive group at the 30-day assessment, with an expected n of 114. With $\alpha = .05$

for a two-sided test, power is at least .80 to detect an $r \geq 0.26$, an association approaching medium strength. The analyses with the least power will be for the nonintensive group at the 180-day assessment. With $\alpha = .05$ for a two-sided test, power is at least .80 to detect an $r \geq 0.36$, an association greater than medium in strength.

Training of Staff

Dr. Tinsley will train her research assistant to obtain consent, administer questionnaires, perform frailty evaluations, and enter data through review of the medical record.

Fidelity and Integrity of the Data

Each subject will have their questionnaires kept confidential by assignment of a number, and data will be extrapolated to Excel spreadsheets and coded by patient identification number only to ensure patient confidentiality. Data will be double checked for accuracy by research staff.

Potential Problems and Alternative Strategies

A potential problem with this study is attrition due to early death from AML or the treatment. This can be overcome by accruing more subjects and may extend the time needed to complete the study. The pilot study was composed of predominantly White, male subjects. This will be addressed by recruiting equal numbers of male and female subjects of diverse ethnic backgrounds.

Expected Outcomes

This study will provide the missing information for patients and caregivers with AML so that QOL data can provide information to make an individualized treatment choice, assisting them with aligning their treatment with goals for end-of-life care, whether they are focused on survival or quality of life.

Timeline

It is anticipated that this prospective study will take approximately 2.5 years for collection of data, followed by analysis and decision modeling. During the last 6 months, a manuscript will be prepared on decision modeling with the identified significant factors.

Future Directions

The model will then be tested for evaluation of accuracy. Future endeavors include a randomized controlled trial incorporating the model into the routine care of older AML patient to test whether it aligns patient preference with treatment compared with usual care. ●

Acknowledgment

Acknowledgment of funding: K23NR018488-03.

Disclosure

The author has no conflicts of interest to disclose.

References

Alibhai, S. M. H., Breunis, H., Matelski, J., Timilshina, N., Kundra, A., Lee, C.-H., & Li, M. (2020). Age-related cytokine effects on cancer-related fatigue and quality of life in acute myeloid leukemia. *Journal of Geriatric Oncology*, *11*(3), 402–409. https://doi.org/10.1016/j.jgo.2019.04.009

Bryant, A. L., Drier, S. W., Lee, S., & Bennett, A. V. (2018). A systematic review of patient reported outcomes in phase II or III clinical trials of myelodysplastic syndromes and acute myeloid leukemia. *Leukemia Research*, *70*, 106–116. https://doi.org/10.1016/j.leukres.2018.06.006

Bryant, A. L., Walton, A. L., Shaw-Kokot, J., Mayer, D. K., & Reeve, B. B. (2015). Patient-reported symptoms and quality of life in adults with acute leukemia: A systematic review. *Oncology Nursing Forum*, *42*(2), E91–E101. https://doi.org/10.1188/15.onf.e91-e101

Cannella, L., Caocci, G., Jacobs, M., Vignetti, M., Mandelli, F., & Efficace, F. (2015). Health-related quality of life and symptom assessment in randomized controlled trials of patients with leukemia and myelodysplastic syndromes: What have we learned? *Critical Reviews in Oncology Hematology*, *96*(3), 542–554. https://doi.org/10.1016/j.critrevonc.2015.07.012

Cella, D. (1994). Quality of life: Concepts and definition. *Journal of Pain and Symptom Management*, *9*(3), 186–192. https://doi.org/10.1016/0885-3924(94)90129-5

Cella, D., Jensen, S. E., Webster, K., Du, H., Lai, J.-S., Rosen, S. T.,...Yount, S. (2012). Measuring health-related quality of life in leukemia: The Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) Questionnaire. *Value in Health*, *15*(8), 1051–1058. https://doi.org/10.1016/j.jval.2012.08.2210

Click, Z. R., Seddon, A. N., Bae, Y. R., Fisher, J. D., & Ogunniyi, A. (2018). New Food and Drug Administration-approved and emerging novel treatment options for acute myeloid leukemia. *Pharmacotherapy*, *38*(11), 1143–1154. https://doi.org/10.1002/phar.2180

Cogle, C. R. (2015). Incidence and burden of the myelodysplastic syndromes. *Current Hematologic Malignancy Reports*, *10*(3), 272–281. https://doi.org/10.1007/s11899-015-0269-y

Covvey, J. R., Kamal, K. M., Gorse, E. E., Mehta, Z., T. Dhumal, Heidari, E.,...Zacker, C. (2019). Barriers and facilitators to shared decision-making in oncology: A systematic review of the literature. *Supportive Care in Cancer*, *27*(5), 1613–1637. https://doi.org/10.1007/s00520-019-04675-7

Deschler, B., Ihorst, G., Platzbecker, U., Germing, U., März, E., de Figuerido, M.,...Lübbert, M. (2013). Parameters

detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. *Haematologica*, *98*(2), 208–216. https://doi.org/10.3324/haematol.2012.067892

Döhner, H., Weisdorf, D. J., & Bloomfield, C. D. (2015). Acute myeloid leukemia. *New England Journal of Medicine*, *373*(12), 1136–1152. https://doi.org/10.1056/nejmra1406184

Hack, T. F., Degner, L. F., & Parker, P. G. (2005). The communication goals and needs of cancer patients: A review. *Psycho-Oncology*, *14*(10), 831–845. https://doi.org/10.1002/pon.949

Howell, D., Wang, H.-I., Smith, A., Howard, M., Patmore, R., & Roman, E. (2013). Place of death in haematological malignancy: Variations by disease sub-type and time from diagnosis to death. *BMC Palliative Care*, *12*, 4. https://doi.org/10.1186/1472-684x-12-4

Howell, D. A., Wang, H.-I., Roman, E., Smith, A. M., Patmore, R., Johnson, M. J.,...Howard, M. (2017). Preferred and actual place of death in haematological malignancy. *BMJ Supportive & Palliative Care*, *7*(2), 150–157. https://doi.org/10.1136/bmjspcare-2014-000793

Institute of Medicine. (2013). *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis*. Washington, DC: The National Academies Press. https://doi.org/10.17226/18359.

Joseph-Williams, N., Elwyn, G., & Edwards, A. (2014). Knowledge is not power for patients: A systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. *Patient Education and Counseling*, *94*(3), 291–309. https://doi.org/10.1016/j.pec.2013.10.031

Juliusson, G., Antunovic, P., Derolf, A., Lehmann, S., Möllgård, L., Stockelberg, D.,...Höglund, M. (2009). Age and acute myeloid leukemia: Real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*, *113*(18), 4179–4187. https://doi.org/10.1182/blood-2008-07-172007

Kantarjian, H. M., Ravandi, F., O'Brien, S., Cortes, J. E., Faderl, S., Garcia-Manero, G.,...Freireich, E. J. (2010). Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood*, *116*(22), 4422–4429. https://doi.org/10.1182/blood-2010-03-276485

Klepin, H. D., Rao, A. V., & Pardee, T. S. (2014). acute myeloid leukemia and myelodysplastic syndromes in older adults. *Journal of Clinical Oncology*, *32*(24), 2541–2552. https://doi.org/10.1200/jco.2014.55.1564

Korol, E. E., Wang, S., Johnston, K., Ravandi-Kashani, F., Levis, M. J., & Van Nooten, F. (2017). Health-related quality of life of patients with acute myeloid leukemia: A systematic literature review. *Oncology and Therapy*, *5*(1), 1–16. https://doi.org/10.1007/s40487-016-0039-6

Krug, U., Röllig, C., Koschmieder, A., Heinecke, A., Sauerland, M. C., Schaich, M.,...German Acute Myeloid Leukaemia Cooperative Group and the Study Alliance Leukemia Investigators. (2010). Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: A web-based application for prediction of outcomes. *The Lancet*, *376*(9757), 2000–2008. https://doi.org/10.1016/s0140-6736(10)62105-8

Leach, M., Kowgier, M., Kermalli, H., Schattner, A., Gupta, V., Minden, M.,...Alibhai, S. M. (2006). Quality of life (QOL) of older adults with acute myeloid leukemia (AML): Effects of treatment and time. *Journal of Clinical Oncology*, *24*(18_suppl), 6566. https://doi.org/10.1200/jco.2006.24.18_suppl.6566

LeBlanc, T. W., & Abernethy, A. P. (2013). Quality of life in higher resolution: The next generation of comparative effectiveness research in malignant hematology. *Haematologica*, *98*(6), 823–824. https://doi.org/10.3324/haematol.2013.085787

LeBlanc, T. W., & Erba, H. P. (2019). Shifting paradigms in the treatment of older adults with AML. *Seminars in Hematology*, *56*(2), 110–117. https://doi.org/10.1053/j.seminhematol.2019.02.002

Master, S., Mansour, R., Devarakonda, S. S., Shi, Z., Mills, G.,...Shi, R. (2016). Predictors of survival in acute myeloid leukemia by treatment modality. *Anticancer Research*, *36*(4), 1719–1727. https://pubmed.ncbi.nlm.nih.gov/27069151/

Mayer, J., Arthur, C., Delaunay, J., Mazur, G., Thomas, X., Wierzbowska, A.,...Kantarjian, H. M. (2014). Multivariate and subgroup analyses of a randomized, multinational, phase 3 trial of decitabine vs treatment choice of supportive care or cytarabine in older patients with newly diagnosed acute myeloid leukemia and poor- or intermediate-risk cytogenetics. *BMC Cancer*, *14*, 69. https://doi.org/10.1186/1471-2407-14-69

Mead, E. L., Doorenbos, A. Z., Javid, S. H., Haozous, E. A., Alvord, L. A., Flum, D. R., & Morris, A. M. (2013). Shared decision-making for cancer care among racial and ethnic minorities: A systematic review. *American Journal of Public Health*, *103*(12), e15–e29. https://doi.org/10.2105/

Miller, K. A., Siegel, R. L., Lin, C. C., Smith, A. B., Kramer, J. S., Rowland, J. H.,...Jemal, A. (2016). Cancer treatment and survivorship statistics, 2016. *CA: A Cancer Journal for Clinicians*, *66*(4), 271–289. https://doi.org/10.3322/caac.21349

Musarezaie, A., Khaledi, F., Esfahani, H. N., & Ghaleghasemi, T. M. (2014). Factors affecting quality of life and fatigue in patients with leukemia under chemotherapy. *Journal of Education and Health Promotion, 2014*, 3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113984/

National Cancer Institute. (2018). SEER Cancer Statistics Review (CSR) 1975-2014. https://seer.cancer.gov/archive/csr/1975_2014/

National Cancer Institute. (2020). SEER Cancer Statistics Review (CSR) 1975-2016. https://seer.cancer.gov/archive/csr/1975_2016/

National Comprehensive Cancer Network. (2016). NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. V3.2016. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

National Comprehensive Cancer Network. (2018). NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. V1.2018. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Ossenkoppele, G. J., & Löwenberg, B. (2015). How I treat the older patient with acute myeloid leukemia. *Blood*, *125*(5), 767–774. https://doi.org/10.1182/blood-2014-08-551499

Rood, J., Nauta, I. H., Lissenberg-Witte, B. I., Stam, F., Flor-

ence, Manenschijn, A.,...Zweegman, S. (2017). Shared decision-making and providing information among newly diagnosed patients with hematological malignancies and their informal caregivers: Not "one-size-fits-all." *Psycho-Oncology*, *26*(12), 2040–2047. https://doi.org/10.1002/pon.4414

Scherber, R. M., Geyer, H. L., & Mesa, R. A. (2014). Quality of life in MPN comes of age as a therapeutic target. *Current Hematologic Malignancy Reports*, *9*(4), 324–330. https://doi.org/10.1007/s11899-014-0239-9

Siegel, R. L., Miller, K. A., & Jemal, A. (2019). Cancer statistics, 2019. *CA: A Cancer Journal for Clinicians*, *69*(1), 7–34. https://doi.org/10.3322/caac.21551

Silverman, L. B., Demakos, E. P., Peterson, B. L., Kornblith, A. B., Holland, J. C., Odchimar-Reissig, R.,...Holland, J. F. (2002). Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the cancer and leukemia group B. *Journal of Clinical Oncology*, *20*(10), 2429–2440. https://doi.org/10.1200/jco.2002.04.117

Stiggelbout, A. M., Pieterse, A. H., & de Haes, J. C. J. M. (2015). Shared decision making: Concepts, evidence, and practice. *Patient Education and Counseling*, *98*(10), 1172–1179. https://doi.org/10.1016/j.pec.2015.06.022

Tariman, J. D., & Szubski, K. (2015). The evolving role of the nurse during the cancer treatment decision-making process: A literature review. *Clinical Journal of Oncology Nursing*, *19*(5), 548–556. https://doi.org/10.1188/15.cjon.548-556

Tinsley, S., Sutton, S. K., Thapa, R., Lancet, J. E., & McMillan, S. C. (2017). Treatment choices: A quality of life comparison in acute myeloid leukemia and high-risk myelodysplastic syndrome. *Clinical Lymphoma, Myeloma & Leukemia*, *17*(Supplement), S75–S79. https://doi.org/10.1016/j.clml.2017.02.016

Walter, R. B., & Estey, E. H. (2015). Management of older or unfit patients with acute myeloid leukemia. *Leukemia*, *29*(4), 770–775. https://doi.org/10.1038/leu.2014.216