A phase II study of the impact of clinicogenetic risk-stratified management on outcomes of acute myeloid leukemia in older patients

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Introduction

Acute myeloid leukemia (AML) is among the most common hematologic malignancies in adults and is commonly diagnosed in sixth or seventh decades of life. AML accounts for approximately 10,000 deaths in the United States every year. Patients with AML are categorized into good, intermediate and high-risk AML based on cytogenetic criteria put forth by the 2017 European LeukemiaNet (ELN) criteria.

The management of AML is complex in older patients because of associated comorbidities, intolerance to high-dose chemotherapy and high-risk tumor biology. For example, in real world practice, over one-third of patients aged 60 years and older do not receive initial chemotherapy for AML. Consequent to such complexities of AML in older patients and current practice patterns, only 10-20% of patients are alive at 3-5 years in real world. Longer-term survival has not improved significantly in last few decades. Poor survival of older patients with AML may be improved with refined risk-stratification and therapy selection strategies, integration of principles of geriatric medicine, and use of effective but low intensity and novel therapies. In 2017, FDA approved gemtuzumab ozogamicin (a humanized CD-33 directed monoclonal antibody-drug conjugate), CPX-351 (liposomal preparation of anthracycline and cytarabine) and midostaurin (FLT3 inhibitor in patients with FLT3 mutated AML) in initial management of AML. Gemtuzumab ozogamicin is approved for CD-33 positive AML (blasts from AML patients are generally CD33 positive), however, the survival benefit with its use is the highest among patients with good risk AML. CPX-351 is FDA-approved (because of survival benefit over 7+3) for patients with prior exposure to chemotherapy or radiation, or those with certain genetic markers (AML with myelodsyplasia-related changes, as defined by WHO). The addition of FLT3 inhibitor midostaurin in FLT3 mutated patients is also associated with survival benefit. In 2018, the FDA approved venetoclax (accelerated approval) (inhibits the anti-apoptotic protein BCL-2) and glasdegib (small molecule inhibitor of the Hedgehog pathway) for AML. Venetoclax received full FDA approval in 2020 in combination with low dose cytarabine (LDAC) or hypomethylating agents, decitabine or azacitidine.(14-16) Glasdegib is approved in combination with LDAC.

In older patients with AML, practical and rational therapy selection is crucial to receive chemotherapy most likely to benefit an individual patient. Select patients are able to tolerate intensive therapy and achieve high rates of complete remission and long-term survival. Such patients are likely to benefit from intensive chemotherapy. Conversely, many older patients have significant comorbidities requiring multiple medications, cognitive impairment, or malnutrition, and are not physically fit to reap the benefit of intensive chemotherapy. The use of intensive chemotherapy in such patients may result in significant toxicities, poor quality of life, deterioration in physical and neurocognitive status and high early mortality. Such patients may be better served with low intensity chemotherapy rather than intensive chemotherapy. Hence, individualized therapy selection should balance both anticipated benefits and risks of toxicities.

The current approach for therapy selection is largely subjective based on chronological age, performance status and/or comorbidities, and does not clearly identify patients who should undergo or forego intensive chemotherapy. Additionally, for many older patients, except for those with good-risk cytogenetic, the goal of initial chemotherapy should be to allow eligible patients to undergo allogeneic hematopoietic cell transplant because transplant, compared to chemotherapy alone, because transplant offers a significantly higher possibility of long-term disease control in high-risk patients. The benefit of transplant is higher in patients who achieve complete remission without significant decline in functional status. The use of intensive

chemotherapy in older patients may be associated with a risk of functional decline and toxicities that may preclude from the safe use of allogeneic transplant. Until recently, low intensity chemotherapy options resulted in low rates of complete remission and a small probability of undergoing an allogeneic transplant. The outcomes of older patients with high-risk AML can improve with enhanced risk-stratification and therapy selection strategies, and with the use of low intensity combination chemotherapy in patients who are not fit to receive intensive chemotherapy.

Comprehensive geriatric assessment offers a thorough assessment of multiple health domains including comorbidities, polypharmacy, cognitive, nutritional, psychological, functional and social status. Such multidimensional assessment based on geriatric principles is an important tool that can improve risk-stratification and therapy selection in older patients. This approach provides a deeper understanding of the biological age and physical fitness of patients, and anticipated tolerance to chemotherapy. In older patients with AML, previous studies have demonstrated that comprehensive geriatric assessment is feasible, uncovers significant functional impairments and predicts toxicities and overall survival. Hence, geriatric assessment is considered superior to therapy allocation based on assessment of age and performance status. Geriatric assessment-guided therapy allocation has been demonstrated to be feasible in older patients with lung cancer and was shown to reduce toxicities compared to therapy allocation based on age and performance status. Based on this rationale, the NCCN guidelines and Cancer and Aging Research Group recommend integrating geriatric assessment in therapeutic decision-making.

Studies in AML have clearly demonstrated the influence of leukemia cytogenetics on the probability of complete remission and survival with intensive chemotherapy. Good-risk AML in fit older patients is associated with a high complete remission rate (up to 80%) and survival (60% at 2 years and 40% at 5 years) when treated with intensive chemotherapy such as anthracycline and cytarabine (7+3), hence such patients are good candidates for intensive chemotherapy. The outcomes of older patients, who are unfit, or have high-risk AML are poor with chemotherapy alone. In these patients, at best, complete remission rates are 30-60%, induction mortality is high (10-40% depending on age and performance status), and long-term survival is less than 10-20%. Although beneficial, allogeneic transplant is not feasible in many older patients, in part because of induction mortality and functional decline from intensive chemotherapy. Recently, CPX- 351 has demonstrated survival benefit over 7+3 for patients with prior exposure to chemotherapy or radiation, or those with certain genetic markers (AML with myelodsyplasia-related changes, as defined by WHO. For this reason, CPX-351 received FDA approval in these subsets of patients.

The use of hypomethylating agents such as decitabine therapy for 5 days, or 7-day course of azacitidine has been extensively studied in older unfit patients with AML. In these studies, hypomethylating agents have improved survival despite a lower probability of complete remission with hypomethylating agents. Importantly, hypomethylating agents such as decitabine therapy results in comparable remission rate within different risk categories of AML, thus indicating that such an approach may be particularly of value in high-risk AML. In more recent years, venetoclax is approved in combination with low dose cytarabine (LDAC) or hypomethylating agents, decitabine or azacitidine; such combination increases the rates of remission as well as survival. The use of newer low intensity chemotherapy combinations in unfit older patients or those with high-risk AML, with complete remission rate largely comparable to intensive chemotherapy, may increase tolerability, and reduce the risk of decline in quality of

life, and cognitive status. This is particularly important for older patients who frequently value maintenance of quality of life and cognitive status over living with functional or cognitive impairment.

Given the powerful impact of leukemia cytogenetics and functional status determined by geriatric assessment on outcomes, we aim to integrate these multidimensional assessments into clinicogenetic risk-stratification strategy, as highlighted in the schema of this study. While the cytogenetic risk category can provide a probability to achieve complete remission with chemotherapy, the findings of geriatric assessment can predict anticipated toxicity risk. Thus, a combination of clinical parameters such as level of fitness of patients as measured by geriatric assessment, and cytogenetic features of leukemia can provide a strategy to individualize therapy selection. The aim of such individualized therapy is to optimize the benefit of chemotherapy in patients most likely to benefit from chemotherapy while reducing the risk of serious toxicities because of intolerance to chemotherapy.

Objectives

Primary objective:

1. To determine the rate of complete remission and 90-day mortality in older patients (≥60 years) with newly diagnosed acute myeloid leukemia (AML), who receive clinicogenetic risk-stratified therapy allocation.

Secondary objectives:

1. To determine the rate of complete remission and 90-day mortality in subsets of older patients who receive intensive and low-intensity chemotherapy.

2. To assess the impact of baseline functional status (measured by geriatric assessment) on mortality in older patients, who receive clinicogenetic risk-stratified therapy allocation.

3. To determine the symptom burden/quality of life, and functional status at diagnosis and following initiation of chemotherapy.

4. To determine proportion of patients with impairments detected by geriatric assessment.

5. To calculate the percentage of older patients who receive allogeneic stem cell transplant during the study period.

6. To assess overall survival at 1-year for the entire cohort of older patients.

Sample Size

The study will include a target total of 75 cases of newly diagnosed AML (approximately 15-20 cases per year for 4-5 years). An optimal Simon two-stage design was used to test the null hypothesis that 60% versus the alternative of 75% will be alive at 3 months. A sample size of 67 patients will have a minimum power to detect a difference of 80%, and a significance level of

0.05. Accounting for an attrition rate of 10%, a total of 75 patients will be enrolled. PASS 11 software was used to conduct all sample size analyses.

Methods

This is a phase II trial for patients with AML. Eligible patients will undergo risk-stratification based on geriatric assessment and cytogenetic features. This is done at enrollment, then again at 30 & 90 days after chemotherapy. Cytogenetic analysis will be done at enrollment as clinically indicated per current standard of care for management of patients with AML. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) and Montreal Cognitive Assessment (MOCA) which detects mild cognitive impairment will be completed at enrollment and 10, 30 & 90 days after chemotherapy.

Participants assigned to the intensive group will receive cytarabine intravenously (IV) on days 1-7 and idarubicin over 10-15 minutes on days 1-3 (7+3), or liposome-encapsulated daunorubicin-cytarabine IV over 90 minutes on days 1, 3 and 5. Gemtuzumab or midostaurin are added to 7+3 as per the standard of care. Treatment continues for 1 course in the absence of disease progression or unacceptable toxicity. Participants who go into remission, receive cytarabine IV over 1-3 hours twice daily (BID) on days 1, 3, and 5. Treatment repeats every 4 weeks for 2-4 courses in the absence of disease progression or unacceptable toxicity. Participants treated with liposome-encapsulated daunorubicin-cytarabine receive liposome-encapsulated daunorubicin-cytarabine IV over 90 minutes on days 1 and 3. Treatment repeats every 5-8 weeks for 2 courses in the absence of disease progression or unacceptable toxicity.

Participants assigned to the low-intensity group will receive oral venetoclax and azacitidine IV on days 1-7 or decitabine IV on days 1-5. Alternate standard of care low-intensity therapies are allowed at the discretion of treating physician. Treatment repeats every 4 weeks for 1-4 courses in the absence of disease progression or unacceptable toxicity. Participants who achieve complete remission, receive oral venetoclax and azacitidine IV on days 1-7 or decitabine IV on days 1-5 or other standard of care low-intensity chemotherapy. Treatment repeats every 4 weeks for 3 or more courses in the absence of disease progression, unacceptable toxicity or receipt of allogeneic stem cell transplant.

Comprehensive Geriatric Assessment

Comorbidity: Comorbidity burden will be calculated according to the Hematopoietic Cell Transplantation Comorbidity Index score. It predicts treatment-related mortality and is more sensitive than the Charlson Comorbidity Index in older adults with AML. Many participants may not have undergone a pulmonary function test or an echocardiogram prior to enrollment. In the absence of a known diagnosis of chronic pulmonary obstructive disease or other pulmonary disease, or congestive heart failure, such patients will receive a score of 0 for pulmonary comorbidity and congestive heart failure. The use of prophylactic antibiotics or fevers thought to be possibly related to tumor fever may not be used to assign a score of 1 for infection. A prior diagnosis of solid or lymphoid malignancies but not myelodysplastic syndrome or other myeloid malignancies gets a score of 3 for prior malignancy.

CPX-351, a liposomal preparation of cytarabine and daunorubicin, preferred agent for FDA approved indicationsm, has shown to improve survival over 7+3 among patients who develop

AML following use of chemotherapy or radiation for prior malignancies. Patients treated with CPX-351 are more likely to undergo curative-intent transplant and have lower risk of transplant-related mortality, hence for patients with therapy-related AML, the use of CPX-351 is desirable (11, 12). For these reasons, patients with therapy-related AML will need an additional score of 2 (not including a score for a history of prior malignancies) in the Hematopoietic Cell Transplantation Comorbidity Index to be considered vulnerable.

Polypharmacy: The list and the number of medications will be obtained from history and physical exam.

Nutritional status: Mini-nutrition assessment short form is a 6-item screening tool used to evaluate the risk of malnutrition in frail older adults. A score of 11 or less on Mini Nutritional Assessment is considered abnormal.

Functional status: Function will be assessed using Katz Index of activities of daily living (ADL) and Lawton instrumental activities of daily living (IADL). ADLs are functions of bathing, dressing, toileting, transferring, continence and feeding. IADLs are patient's ability to perform complex tasks such as ability to use telephone, shopping, cooking, housekeeping, laundry, driving, medication management, and management of finances. Mobility, balance and lower extremity strength will be assessed with the Short Physical Performance Battery.

Social support: The Medical Outcomes Study Social Function Scale is a survey containing 19 items on emotional/informational, tangible, and affectionate support and positive social interaction.

Psychological status: The Patient Health Questionnaire-9 will be used to assess depression. It includes nine items that cover the diagnostic criteria for major depressive disorder. Although depression is associated with mortality, the presence of depression is captured by the Hematopoietic Cell Transplantation Comorbidity Index. A score of 10 or higher on Patient Health Questionnaire-9 is indicative of major depression.

Cognition: Montreal Cognitive Assessment will be used to screen for cognitive impairment. It assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.)

Geriatric syndromes: Falls in last 6 months, history of dementia or delirium, history of urinary or stool incontinence.

Cytogenetic Analysis

In this study, the results of conventional karyotyping/fluorescence in situ hybridization (FISH) will be used for classification of risk categories since molecular mutation panel generally take more than 7-10 days to results, however, if certain molecular mutation results (e.g. NPM1 and FLT3 ITD mutations) are available at the time of risk categorization and decision-making regarding low intensity and intensive chemotherapy, the results will be taken into consideration. Since allelic ratio is not performed in routine practice, if FLT3 ITD is present, patients will be categorized as intermediate risk category. If cytogenetic and/or FISH testing cannot be performed despite reasonable attempt because of reasons such as failure to grow cells/induce mitosis, lack of suitable specimens, patients will be categorized as intermediate-risk AML.

Adverse Events

All adverse events will be reported from the time of initiation of study drug until 30 days after last administration of study medication, or in case of low intensity therapy, 30 days after the end of 3rd cycle or last cycle (if stopped prior to the 3rd cycle) of venetoclax-hypomethylating combination or low-intensity therapy. Adverse event and serious adverse events will be followed until baseline, ≤ grade 1 levels, death, or until no further improvement is reasonably expected. Toxicity will be assessed using the revised NCI CTCAE version 4.03. This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

Deaths occurring within 30 days of study treatment regardless of relationship will be reported Participants will be monitored from initiation of study drug until 30 days after last administration of study drug. All adverse events recorded during the study will be summarized by individual subject. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by severity and type of adverse event. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will be recorded.

Stopping Rule

The therapies used in this study are considered standard of care. A risk stratification strategy is considered necessary for therapy allocation even outside of a clinical trial. Significant toxicities are frequently observed in clinical practice in this patient population. With this background, the proposed two-stage design has an expected sample size of 39.35 and a probability of early termination of 0.691 under the conditions specified in the sample size justification. After testing the intervention on 27 evaluable participants in the first stage, the trial will be halted pending DSMC review if 10 or more participants die within 3 months of diagnosis of AML. Participants, who are enrolled in the study, and are tolerating the study drug may continue the drug. If the trial goes on to the second stage, a total of 67 evaluable participants will be studied. If more than 21 participants die by 3 months of diagnosis of AML, the intervention will be rejected. For the purpose of stopping rules, participants will be considered evaluable if they receive at least one dose of study medication and if alive, maintain study follow-up for at least one month after enrolling to the study.

Follow-up

Participants will be evaluated for disease status, survival, quality of life and neurocognitive status for 90 days after completion of treatment, then followed for survival for two years.

Data Analysis

Data will be descriptively summarized using frequencies and percentages. A p-value less than 0.05 will be considered statistically significant unless otherwise specified. All analyses will be performed based on intent-to-treat principle. The method of inversion will be used to generate an interval estimate for the proportion of 90-day mortality. The association between functional status (fit, or vulnerable based on geriatric assessment), and 90-day mortality will be explored using a chi-square test. The proportion (and associated 95% confidence interval) of participants

with impairments across various domains of geriatric assessment will be presented. Composite scores from EORTC QLQ-C30 version 3.0, will be used to determine quality of life status. A generalized linear mixed model will be utilized to evaluate changes in quality of life over time. Composite scores, as determined by MOCA test, will be utilized to determine neurocognitive status. Overall survival is defined as the time from date of diagnosis to date of death due to any cause. If a subject is not known to have died, survival will be censored at the date of last contact. The Kaplan-Meier method will be used to estimate the survival distribution. OS rates at 1 and 2 years will be provided as well as 95% CI. Descriptive statistics will be used to compare participant characteristics between groups. Mean, standard deviation (SD), median and range will be reported for continuous variables, and they will be compared with t-tests or the Wilcoxon rank sum test. Frequencies and percentages will be used to describe categorical variables, and they will be compared between groups with chi-square tests.