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Quality of Life in Vyxeos-Treated Patients with Acute Myeloid Leukemia

Research Article

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Abstract

Background

Therapy-related acute myeloid leukaemia (t-AML) and AML with myelodysplasia-related changes (AML-MRC) are rare AML subtypes with poor clinical outcomes. Standard of care (SoC) includes induction chemotherapy with 7 continuous days of cytarabine + an anthracycline during the first 3 days, known as the "7+3" regimen. Aggressive treatment improves survival rates, but is associated with prolonged hospitalization, severe adverse effects, and decreased quality of life (QoL). Vyxeos is a fixed combination of daunorubicin and cytarabine with a synergistic 1:5 molar ratio encapsulated in a liposome. The combination is indicated for the treatment of newly diagnosed therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and paediatric patients 1 year and older. Vyxeos has shown improved clinical outcomes compared to 7+3 treatment; however, the impact of Vyxeos on patient QoL remains unknown. To address this knowledge gap, this real-world study was designed to explore the impact of Vyxeos versus 7+3 treatment on QoL among patients diagnosed with t-AML or AML-MRC.

Methods

This prospective, multi-center, real-world, U.S. study assessed QoL of patient's ≥18 years old from AML diagnosis (baseline) up through Week 26 using the AML-QoL questionnaire. Patient-level disease and treatment characteristics were abstracted from medical chart review using a standardized case report form. The primary outcome was to compare change in QoL from baseline to completion of first induction cycle (count recovery) in patients treated with Vyxeos or the 7+3 regimen.

Results

A total of 11 patients were enrolled across 4 academic cancer centres between August 2020 through May 2022. Challenges in recruitment impacted this study's ability to make QoL assessments in a sufficient number of patients. Within the Vyxeos cohort (n=8), 3 patients (38%) had AML-QoL scores at baseline and count recovery: 2 patients (66%) had a clinically meaningful decrease (-14.2 and -11.4), and 1 patient (33%) had a clinically meaningful increase (+27.1). Within the 7+3 cohort (n=3), 2 patients (67%) had AML-QoL scores at baseline and count recovery, both with a clinically meaningful decrease in scores (-25.6 and -41, respectively).

Conclusions

Among the 5 patients that completed surveys at baseline and count recovery, study results showed a greater decrease (worsening) in AML-QoL scores for patients receiving induction therapy with the 7+3 SoC regimen compared to Vyxeos following completion of one induction cycle, among patients with tAML or AML-MRC. Future real-world studies with larger sample sizes are needed to verify these findings.

Keywords: AML; t-AML; AML-MRC; QoL; Vyxeos; 7+3; RWD; liposomal

Introduction

Acute myeloid leukemia (AML) is a rapidly progressing and aggressive bone marrow cancer that accounts for 25% of adult Leukemia worldwide with an estimated 5-year survival of 30.5% [1–3]. According to the National Cancer Institute, there were 20,050 new cases of AML and 11,540 deaths from AML in 2022, with a median age of diagnosis of 68 years old [1]. AML is associated with significant economic burden and estimated total costs in the U.S. range from $0.5 to $1.5 billion for patients over 65 and under 65 years, respectively [4]. The current standard of care for AML is induction chemotherapy consisting of 7 continuous days of cytarabine (nucleoside metabolic inhibitor), combined with an anthracycline (topoisomerase II inhibitor) during the first 3 days, also known as the "7+3" regimen [3-5] .other treatment options include decitabine, azacitadine, low-dose cytarabine, venetoclax, targeted therapies (i.e., FMS-like tyrosine kinase 3 [FLT3] and isocitrate dehydrogenase [IDH] inhibitors), and best supportive care depending. Aggressive treatment of AML improves survival rate, but is associated with prolonged hospitalization, severe adverse effects, reduced physical function, and decreased quality of life (QoL) [6-7] .Previous research has demonstrated reduced QoL for patients with AML shortly after diagnosis; fatigue, anxiety, and the impact of AML on family members most significantly impacted QoL scores. [8].

While a variety of patient-reported outcome (PRO) instruments to measure QoL in cancer patients exist, few are designed specifically for Patients with AML [8]. A common instrument for measuring PROs in people with cancer is the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). The EORTC QLQ-C30 is a validated 30-question survey that covers five domains (physical, role function, emotional, social, and cognitive) [9] .However, this survey was developed for patients with lung cancer and has not been validated specifically for AML [8] .Moreover, there is a lack of consensus concerning which QoL PRO instrument to use in AML clinical trials [10]. To address these needs, Buckley et al. developed an AML-specific QoL instrument called the AML-QoL. This PRO instrument consists of 40 questions covering 5 positive concepts and 21 negative concepts. Positive concepts include family support, having a positive attitude or hope for the future, friends or community, trust in the medical team, and participation in activities or exercise. Negative concepts include but are not limited to fatigue, fear/anxiety, pain, sleep problems, confusion/memory impairment, emotional isolation, loss of hope, and inability to work.

Therapy-related AML (t-AML) is an often-fatal AML subtype resulting from cytotoxic and/or radiation therapy and accounts for only 7-8% of all AML cases. [11-19] while the ethology is unclear, mutational events triggered by chemotherapy, radiation therapy, or immunosuppressive therapy may be the cause [11]. Compared to de novo AML, t-AML is associated with shorter survival because of prolonged and profound cytopenia, malignancies, and chemotherapy resistance. AML with myelodysplasia-related changes (AML-MRC is another AML subtype associated with a poor prognosis. AML-MRC is characterized by at least 20% myoblasts and various dysplastic morphologies in bone marrow and accounts for 25–34% of all AML subtypes [12-20]. Studies have suggested that dysplastic morphological changes in granulocytes are associated with reduced complete remission rates and event-free survival [13-14]. Treatment for t-AML and AML-MRC includes 7+3 induction and consolidation treatment. Vyxeos is a fixed combination of daunorubicin and cytarabine with a synergistic 1:5 molar ratio encapsulated in a liposome; indicated for the treatment of newly diagnosed therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and paediatric patients 1 year and older [5,15] .Vyxeos is the only NCCN guideline-recommended induction therapy (category 1) [5].

Vyxeos has demonstrated better overall survival (9.6 vs. 5.9 months, p=0.005) and complete response rate (47.7% vs 33.3%, p=0.016) compared to standard cytarabine and daunorubicin 7+3 therapy in patients with t-AML or AML-MRC [15-16]. Similarly, evidence from clinical trials has shown favourable effects on patient-reported QoL with Vyxeos-therapy compared to the 7+3 regimen [26-27] .However, studies evaluating the impact of Vyxeos treatment on patient QoL in a real-world setting are lacking. To address this knowledge gap, the primary objective of this study was to evaluate change in QoL using an AML-specific PRO instrument among newly diagnosed t-AML or AML-MRC patients following completion of first induction cycle (count recovery). Additionally, this study assessed QoL and treatment tolerability using general cancer PRO instruments.

Materials & Methods

Study Design

This was a prospective, multi-center, real-world QoL survey study. Quality of life was measured using three PRO instruments (AML-QoL, EORTC QLQ-C30, and PRO-CTCAE) distributed to patients at pre-specified intervals including AML diagnosis/Week 0 (baseline), Week 4 (count recovery), and Week 26 (final follow-up). Study outcomes were focused on observed changes from baseline to count recovery. Additionally, patient-level disease and treatment characteristics were abstracted from medical chart review using a standardized case report form (CRF). See Appendix 2 for details.

Study Population

This study included a geographically diverse cohort of adult patients with newly diagnosed t-AML or AML-MRC across four US academic cancer centres. Eligible patients had planned induction treatment with either 7+3 or Vyxeos.

Inclusion/Exclusion Criteria

Included patients were at least 18 years old at diagnosis of AML. Diagnosis was based on World Health Organization (WHO) criteria. AML subtypes of interest included t-AML and AML-MRC. Additionally, all included patients had planned induction treatment with either the 7+3 regimen or Vyxeos. Patients who were diagnosed with acute promyelocytic leukemia (APL), were receiving Vyxeos for any indication other than AML, or had planned induction with any treatment other than 7+3 or Vyxeos were excluded. Additionally, patients who received an additional AML directed therapy (FLT3/IDH/venetoclax) were excluded. See Appendix 1 for additional details.

Site and Subject Recruitment

The Huntsman Cancer Institute (HCI), an Oncology Research Information Exchange Network (ORIEN) member, served as the lead coordinating site for this study through partnership with the Pharmacotherapy Outcomes Research Center (PORC) at the University of Utah. Both ORIEN member-institutions and non-member cancer centres across the US were contacted for participation. Interested sites completed a feasibility survey including AML patient counts.

Recruitment of Study Patients

The study team at each site was led by a haematologist or other health care professional (i.e., nurse, pharmacist) who were supported by research personnel (study coordinators, data analysts) to perform the study. Diagnosis of t-AML or AML-MRC was made by treating clinician. Eligible patients were approached by study coordinators to obtain informed consent and review requirements for study participation. Participating patients received a $20 gift card for each survey completed. A step-by-step patient recruitment and survey dissemination plan is included in Appendix 4.

Data Collection

PRO Instruments

This study used three PRO survey instruments: AML-QoL, EORTC QLQ-C30, and PRO-CTCAE [8, 9, 17]. The AML-QoL instrument consists of 27 questions organized into 7 categories. This instrument includes 5 multi-item domains (physical, social, cognitive, anxiety and mood) a symptom index, and a single-item QoL measure. A Summary Score ranging from 0 to 100 can be calculated based on category scores, with higher scores representing better QoL and less symptomology. The EORTC QLQ-C30 includes 5 functional scales (physical, role, social, emotional, and cognitive functioning), 9 symptom scales (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhoea, constipation, sleep disturbance and quality of life), and a global health status scale. Scores range from 0-100, with higher scores for functional and global health scales indicating better health, and higher scores among symptom scales indicating worse health (higher symptomology). The PRO-CTCAE is focused on the adverse effects/toxicities resulting from cancer therapies and is designed to characterize the severity, frequency, and interference of 78 symptomatic treatment effects. It is scored using a 1-to-5-point Likert scale, with severity from “no symptoms” to “very severe”, frequency from “never” to “almost constantly”, and interference from “not at all” to “very much”. For this study, only a total of 22 questions related to AML-specific treatment toxicities were included from the PRO-CTCAE questionnaire.

Survey Dissemination

Each survey was distributed to enrolled patients at eight predefined intervals over a 26-week period, corresponding to clinical timepoints of a patient’s course of therapy. A comprehensive study calendar and timeline for patient assessment is shown in (Table 1). Surveys were anticipated to take 20-30 minutes to complete, with no time limit. Links

Visit	Screening	Start of Induction	End of Induction	Nadir	Count Recovery (primary time point of interest)	Prior to Cycle 2 of intensive chemotherapy	Post count recovery from consolidation therapy	Prior to transplant or salvage treatment	End of Follow-up*
Week	From 1 week prior to 72 hours post start of induction	Week 1, Day 1	Week 1, Day 7	Week 2 (±5 days)	Week 4 (± 5 days)	Week 6 (±7 days)	Week 10 (±7 days)	Week 18 (±7 days)	Week 26 (±7 days)
Informed consent	X								
Eligibility review	X								
Demographics	X								
Treatment patterns	X	X	X	X	X	X	X	X	X
Medical history	X								
Concomitant meds	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30	X		X	X	X	X	X	X	X
NCI-CTCAE PRO	X		X	X	X	X	X	X	X
AML Survey	X		X	X	X	X	X	X	X

Table 1: Study calendar

to the survey in the Qualtrics platform were distributed electronically via email. All data was de-identified and analysed in aggregated form (Figure 1).

Demographic and Clinical Data

PORC developed a CRF to standardize the data collection process. The CRF was shared with all sites. Study staff at each site collected patient-level demographic data and treatment information at time of screening and at each predefined interval. De-identified patient data was transferred to PORC researchers for analysis. For a complete list of study variables and individual PRO instrument components see Appendix 5.

Data Analysis

Demographics, disease characteristics, and treatment characteristics were summarized and compared using descriptive statistics and provided as means/standard deviations (SD) for patients receiving Vyxeos vs. 7+3 therapy. AML-QoL summary scores were calculated for patients across the study timeframe from baseline by treatment category using methods described by Buckley [8] .Change in summary score at count recovery from baseline was calculated for each patient. EORTC-QLQ-C30 functional, symptom, and global health scores were summarized using means/ standard errors (SE) and compared at baseline and at count recovery. PRO-CTCAE scores were categorized by question type (severity, frequency, and interference) and summarized by counts at baseline and at count recovery.

Results

Study Sites

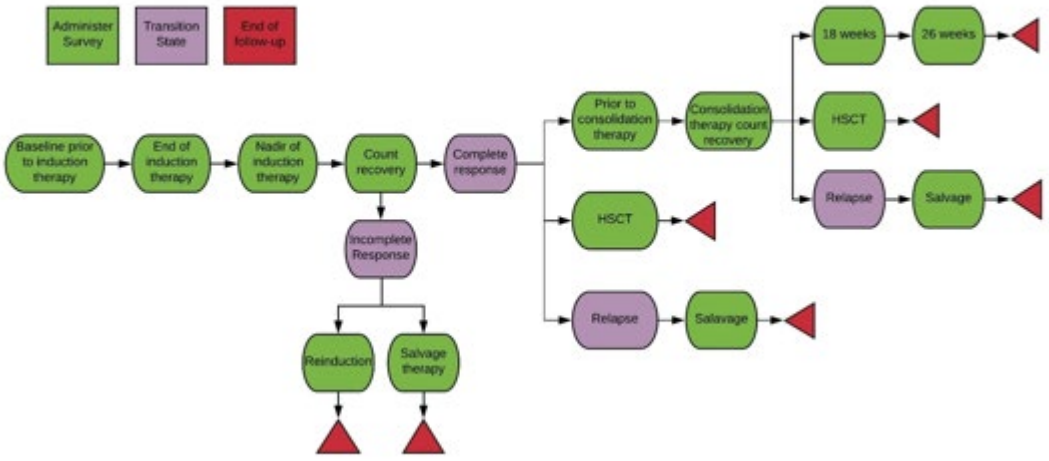
Four academic cancer centres across the U.S. participated in this study: Huntsman Cancer Institute (HCI) at the University of Utah, The James Cancer Hospital at Ohio State University (OSU), Lineberger Comprehensive Cancer Center at the University of North Carolina Chapel Hill (UNC), and Holden Comprehensive Cancer Center at the University of Iowa (UI). The preliminary sample size goal for this study was 100 patients. Due to challenges in recruitment primarily related to study overlap with the COVID-19 pandemic, a total of 11 patients were enrolled for this study: HCI (n=4), OSU (n=5), UNC (n=1), and UI (n=1) between 8/2020 through 5/2022. The slow patient accrual throughout recruitment led to early study closure.

Patient Demographics

Patient demographics are shown in Table 2. Mean age was similar in the Vyxeos and 7+3 cohorts at 57.5 years. Overall, 7 patients (64%) were male. Mean bone marrow blasts at diagnosis was 32.6% (SD: 13) and 57% (SD: 27) for the Vyxeos and 7+3 cohorts, respectively. In the Vyxeos cohort, 88% (n=7) were diagnosed with AML-MRC, and 13% (n=1) with t-AML. In the 7+3 cohort, all patients (n=3) were diagnosed with AML-MRC. Across all patients (n=11), cytogenetic risk per European Leukemia Net guidelines were intermediate (45%) or unfavorable (64%). Among all patients with an available ECOG score (n=10), 80% (n=8) had an ECOG score of ≤ 1 at diagnosis (Table 2).

Treatment Patterns

Patient-level treatment information for patients receiving induction therapy is included in Table 3. Most patients (n=8) received Vyxeos as induction therapy (Vyxeos cohort) and three patients received a traditional 7+3 regimen of cytarabine and an anthracycline (7+3 cohort). No patients in the Vyxeos cohort received re-induction therapy, while 2 (67%) patients in the 7+3 cohort required re-induction (one receiving Vyxeos, and the other midostaurin). Consolidation therapy was received by 6 (75%) patients in the Vyxeos cohort [Vyxeos: n=4 (50%); high dose cytarabine (HiDAC): n=2 (25%)]. One patient (33%) received consolidation therapy in the 7+3 cohort with HiDAC. Following consolidation therapy, 3 (38%) patients received a hematopoietic stem-



HSCT, hematopoietic stem cell transplant

Figure 1: Flow Chart of Survey Dissemination.

Variables	Vyxeos (n=8)	7+3 (n=3)	All included patients (n=11)
Age, mean (SD)	57.5 (11.5)	57.5 (0.7)	57.5 (10.1)
Male, n (%)	6 (75)	1(33)	7 (64)
Comorbidities, n (%)			
Myocardial Infarction	1 (13)	1 (33)	2 (18)
Congestive heart failure	0 (0)	0 (0)	0 (0)
Peripheral vascular disease	0 (0)	0 (0)	0 (0)
Cerebrovascular disease	1 (13)	0 (0)	1 (9)
Chronic Pulmonary Disease	1 (13)	0 (0)	1 (9)
Dementia	0 (0)	0 (0)	0 (0)
Diabetes	0 (0)	1 (33)	1 (9)
Diabetes w/complications	0 (0)	1 (33)	1 (9)
Hemiplegia/paraplegia	0 (0)	0 (0)	0 (0)
Renal disease	1 (13)	0 (0)	1 (9)
Mild liver disease	0 (0)	0 (0)	0 (0)
Moderate/severe liver disease	0 (0)	0 (0)	0 (0)
Peptic ulcer disease	0 (0)	0 (0)	0 (0)
Rheumatologic disease	0 (0)	0 (0)	0 (0)
Bone marrow blasts at diagnosis (%), mean (SD)	32.6 (13)	57 (27)	39 (20)
AML type, n (%)			
AML-MRC	7 (88)	3 (100)	10 (91)
t-AML	1 (13)	0 (0)	1 (9)
Prior exposure to anthracycline, n (%)	0 (0)	0 (0)	0 (0)
Prior exposure to HMA, n (%)	2 (25)	0 (0)	2 (18)
Karnofsky score at diagnosis, n (%)			
0-20%	0 (0)	0 (0)	0 (0)
21-40%	0 (0)	0 (0)	0 (0)
41-60%	1 (13)	0 (0)	1 (9)
61-80%	2 (25)	1 (33)	3 (27)
81-100%	2 (25)	1 (33)	3 (27)
Unknown	3 (38)	1 (33)	5 (45)
ECOG at diagnosis, n (%)			
0	2 (25)	2 (67)	4 (36)
1	3 (38)	0 (0)	4 (36)
2	1 (13)	0 (0)	1 (9)
3	0 (0)	1 (33)	1 (9)
4	0 (0)	0 (0)	0 (0)
Unknown	2 (25)	0 (0)	2 (18)
Cytogenetic risk by European Leukemia Net (ELN), n (%)			
Favorable	0 (0)	0 (0)	0 (0)
Intermediate	3 (38)	2 (67)	5 (45)
Unfavorable	5 (63)	1 (33)	7 (64)

Table 2: Patient Demographics

cell transplantation (HSCT) in the Vyxeos cohort compared to none in the 7+3 cohort (Table 3).

Treatment Response

Following induction therapy, 7 (88%) patients in the Vyxeos cohort achieved complete response (CR), with 4 (50%) patients classified as morphologic CR and 3 (38%) patients as CR with incomplete hematologic recovery (CRi). Among the Vyxeos patients achieving CR, one patient (14%) died shortly after receiving consolidation therapy. One patient (13%) in the Vyxeos cohort failed induction and was subsequently lost to follow-up.

In the 7+3 cohort, one patient (33%) achieved a partial response to induction, with the other two (67%) failing induction. Of these two, one received re-induction therapy with Vyxeos and later achieved a complete response (morphologic CR). The other patient receiving midostaurin failed re-induction and was subsequently lost to follow-up.

Patient Quality of Life Surveys

Among all included patients (n=11), median time spent completing surveys was 12.95 minutes (IQR: 12.96). Survey response rates declined for both Vyxeos and 7+3 treated patients as they moved through their treatments. Weeks 1 and 2 had the highest response rates with 73% (n=8) of all patients completing the surveys. There were no completed surveys for any patients treated with 7+3 following count recovery, and similarly only 3 (38%) Vyxeos treated patients completed surveys following count recovery.

The primary objective of this study was to evaluate the difference in quality of life from baseline to the end of first induction cycle between Vyxeos and 7+3-treated patients. Three Vyxeos patients (P-03, P-05, and P-07) and two 7+3 patients (P-10 and P-11) completed surveys at both baseline and count recovery. The following QoL survey results report the observed differences in scores between these two groups of patients.

AML-QoL

Patient-level AML-QoL summary scores are included in Table 4 and Figure 2. Summary scores are scaled from 0-100, with higher scores representing a higher quality of life. A difference of ~10 points in an AML-QoL summary score is considered a clinically meaningful change [17]. In the Vyxeos cohort (n=3), 2 (66%) had a clinically meaningful decrease (worsening) in AML-QoL score (-14.2 and -11.4), and 1 patient (33%) had a clinically meaningful increase (improvement) in AML-QoL score (+27.1). Within the 7+3 cohort (n=2), both patients showed a clinically meaningful decrease in AML-QoL score (-25.6 and -41) (Figure 2) (Table 4).

PRO-CTCAE

PRO-CTCAE scores for the Vyxeos and 7+3 cohorts are shown in Figure 3. In the Vyxeos cohort (n=3), 1 patient (33%) reported increased severity, frequency, and interference of sadness, discouragement, and anxiety from baseline to count recovery. At baseline, 2 patients (66%) in the Vyxeos cohort reported mild to moderate fatigue; at count recovery all 3 Vyxeos patients reported mild to severe fatigue. In the 7+3 cohort (n=2) at baseline, one patient reported "a little bit" interference of sadness, and no patients reported interference from discouragement, anxiety, or loss of appetite. At count recovery, both 7+3 patients reported "a little bit" to "quite a bit" or interference from sadness and loss

S.NO	Week 0 - Week 6					Week 18	Week 26
	Induction		Cycle 2			Transplant	Final follow-up
Patient ID*	Induction therapy type	Response to induction	Re-induction therapy	Consolidation therapy	Status/response after cycle 2	HSCT type	Status
P-01	Vyxeos	Complete response	→	Vyxeos	Alive in remission	Allogenic	
P-02	Vyxeos	Complete response	→	HiDAC	Death		
P-03	Vyxeos	Complete response	→	Vyxeos	Alive in remission	Allogenic	
P-04	Vyxeos	Complete response	→	Vyxeos	Alive in remission	Autologous	
P-05	Vyxeos	Complete response	→	Vyxeos	Alive in remission	→	Alive in remission
P-06	Vyxeos	Complete response					
P-07	Vyxeos	Complete response	→	HiDAC	Alive in remission		
P-08	Vyxeos	Induction failure					
P-09	7+3	Induction failure	Other**				
P-10	7+3	Partial response	→	HiDAC			
P-11	7+3	Induction failure	Vyxeos	→	Complete response		

*One patient received no therapy and is not included in this table
**Midostaurin & IT methotrexate

Table 3: Treatment Patterns and Responses

of appetite, and 1 patient reporting "a little bit" to somewhat inference from discouragement and anxiety (Figure 3).

EORTC QLQ-C30

Mean EORTC QLQ-C30 functional, symptom, and global health scale at baseline and at count recovery for the Vyxeos (n=3) and 7+3 (n=2) cohorts are shown in Figure 4 and Figure 5. Mean scores decreased (worsened) in four functional domains [physical (-21.7), role (-22.3), emotional (-8.3), and social (-5.6)] from baseline to count recovery for the Vyxeos cohort. In the 7+3 cohort, mean scores decreased in all five functional domains [physical (-40), role (-25), emotional (-25.1), cognitive (-25), and social (-33.4)] from baseline to count recovery. Global health/QoL mean scores increased (improved) slightly by 5.6 points in the Vyxeos cohort, and decreased by 37.5 points in the 7+3 cohort, from baseline to count recovery. There was a 3 to 5-fold greater increase (worsening) for pain and loss of appetite scores in the 7+3 cohort compared to Vyxeos, from baseline to count recovery (Figure 4& 5).

Discussion

Given the small study sample size due to slow patient enrolment across all sites, this study did not detect significant differences in QoL between patients treated with Vyxeos and 7+3. However, the pursuit of QoL outcomes for patients receiving Vyxeos is warranted based on the phase III clinical trial results that found significantly improved overall survival (HR=0.69; P=0.005; median OS 9.56 vs. 5.95 months), EFS (HR=0.74; P=0.021), and CR+CRi response (47.7% vs. 33.3%; P=0.016) among Vyxeos-treated patients compared to 7+3 therapy [16]. The study design and preliminary results of this study are intended to inform future research on the QoL impact of Vyxeos in AML patients.

Patient QoL, as measured by the AML-QoL score, decreased for all but one patient from baseline to count recovery. Notably, patients treated with 7+3 for induction therapy showed a 2 to 4-fold greater decrease in AML-QoL score when compared to Vyxeos-treated patients. These findings suggest that patients with t-AML and AML-MRC may maintain higher QoL with Vyxeos induction therapy when compared to 7+3 induction therapy. A post-hoc analysis of the pivotal phase 3 study that evaluated Vyxeos vs. 7+3 regimen in patients aged 60 to 75 years with newly diagnosed high-risk/secondary AML demonstrated that Vyxeos significantly improved quality-adjusted survival compared to 7+3 therapy using a quality-adjusted time without symptoms of disease or toxicity (QTWiST) analysis [26].Additionally, an exploratory analysis of an ongoing, multi-site clinical trial (NCT02975869) found higher QoL scores among Vyxeos-treated patients compared to 7+3 (FACT-Leu: 118.01 vs 112.56. p=0.44) [27]. Though the trend for improved QoL among Vyxeos-treated patients compared to 7+3 was observed in this study, additional studies with larger sample sizes are needed to verify these findings in real world settings.

This study has several strengths. First, this study is one of the few incorporating an AML-specific PRO instrument in this specific patient population. Most prior studies evaluating QoL in patients receiving treatment for AML utilized nonspecific PRO instruments that are applicable across all cancer types. Second, to the best of our knowledge, no other QoL studies have focused on patients with AML-MRC or t-AML. Compared to de novo AML, patients with AML-MRC and t-AML tend to experience lower remission rates following chemotherapy and a median overall survival of only 9 to 12 months and 10 to 14 months, respectively [20]. Considering the generally poor prognosis associated with these AML subtypes, understanding the clinical impact and patient perspective of commonly used therapies is of great value. Third, this study includes patients from multiple academic cancer centres across the U.S.

This study also had several limitations. Significantly, this study was not able to recruit as many patients as initially expected. A major portion of this study was conducted during

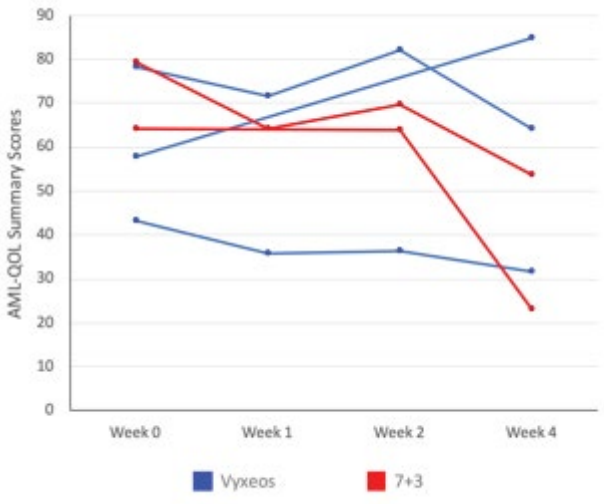
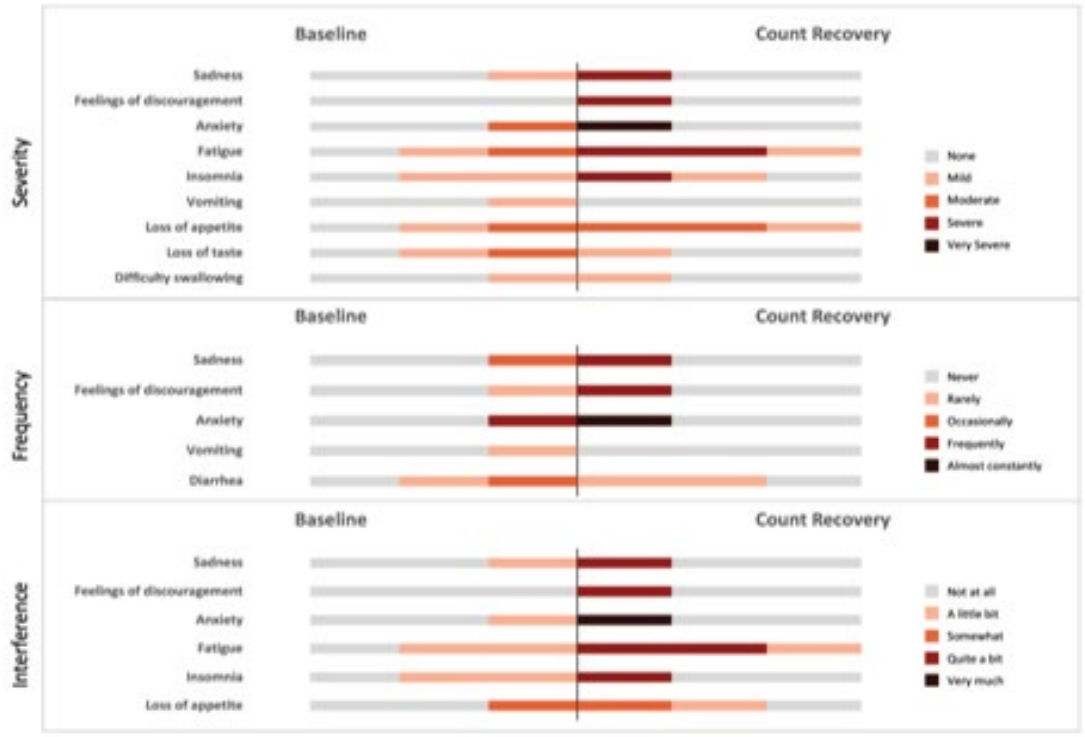
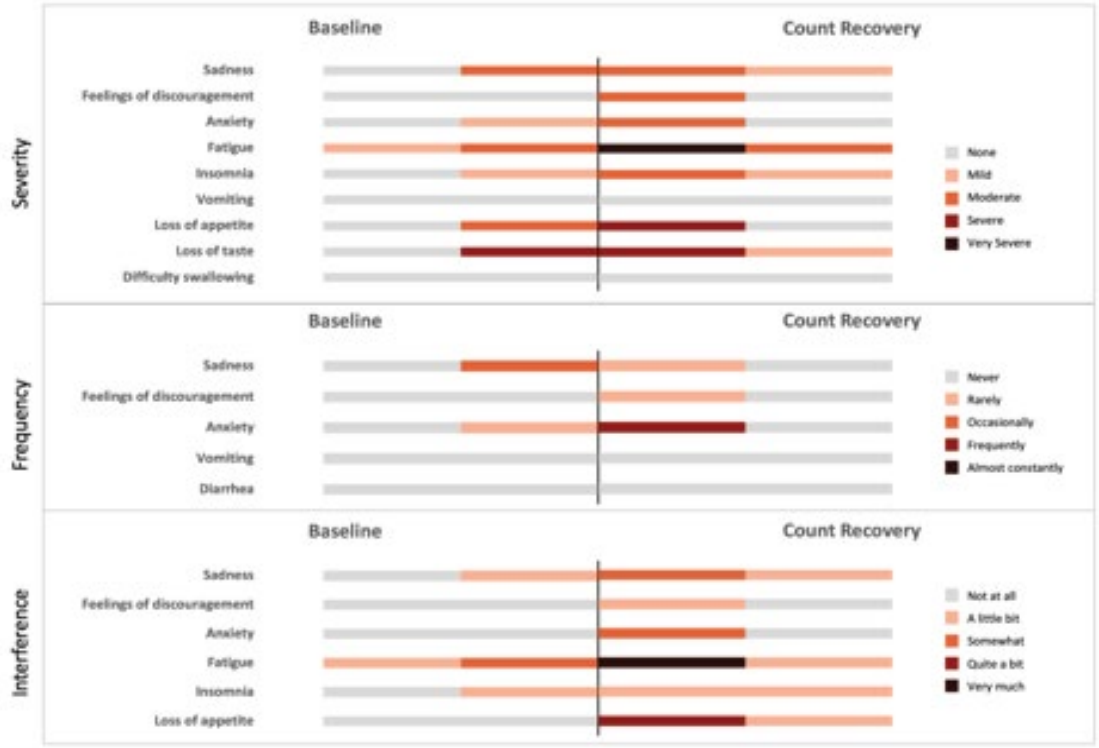


Figure 2: AML-QoL Summary Scores at Baseline and at Count Recovery (Week 4).



A. Vyxeos Cohort (n=3)



B. 7+3 Cohort (n=2)

Figure 3: PRO-CTCAE Symptom Scores.

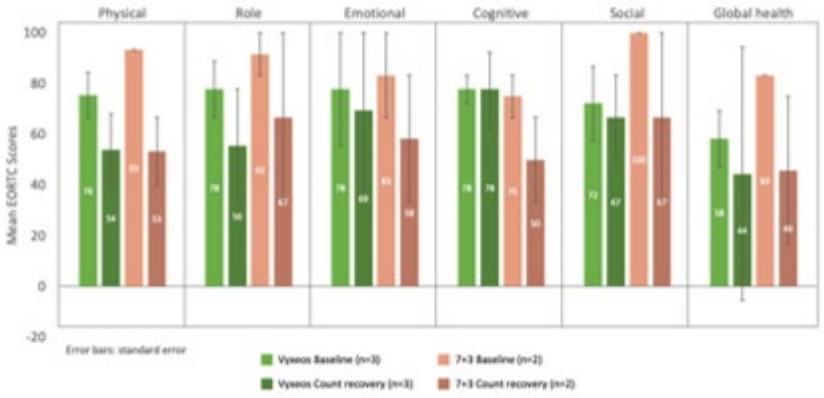


Figure 4: EORTC-QLQ-C30 Functional/ Global Health Scale at Baseline and Count Recovery.

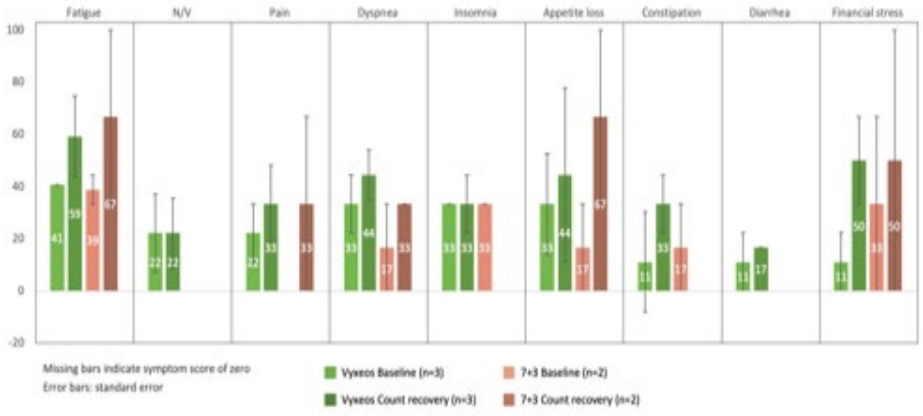


Figure 5: EORTC-QLQ-C30 Symptom Scale at Baseline and Count Recovery.

	Patient ID	Week 0	Week 1	Week 2	Week 4	Week 6	Week 10	Week 18	Week 26	Δ From week 0 – 4
	P-01		55.1	58.5	47.7	53.2	54.9	49.7		
	P-02		62.2	84.7						78.3
Vyxeos	P-03	78.3	71.6	82	64.1			75.5		62.6
	P-04	62.6	49.1							43.1
	P-05	43.1	35.9	36.4	31.7	25.8			29.5	
	P-06		71.3							57.7
	P-07	57.7			84.8					
	P-08		71.3	69.4	39.8	15				79.4
	P-10	79.4	64.1	69.7	53.8					64.2
7+3	P-11	64.2		63.8	23.2					

Values in blue indicate a clinically meaningful (Δ ≥ 10 points) increase in score

Values in red indicate a clinically meaningful (Δ ≥ 10 points) decrease in score.

Table 4: AML-QoL Summary Scores

the COVID-19 pandemic, which resulted in decreased cancer screening, delayed care, and transition to telehealth services for many patients [21-22]. These factors significantly impeded the patient recruitment process. Second, t-AML and AML-MRC are estimated to account for 10% and 24-35% of all AML diagnoses, respectively [23-24] .The lower prevalence of these AML subtypes likely contributed to slow accrual. Further, the treatment paradigm shifted during the course of the study with increased utilization of induction therapies other than 7+3 or Vyxeos, and add-on therapies to induction regimens (i.e., FLT3/IDH/venetoclax), which limited recruitment. Third, survey completion rates among the 12 enrolled patients were lower than anticipated. This could have been due to patient burden/exhaustion resulting from the disease or pandemic-related staffing challenges at each respective site. Moreover, this study used clinical timepoints for survey distribution (i.e., start of induction, count recovery, etc.) instead of defined chronological timepoints. Differences in treatment cycle lengths between Vyxeos and 7+3 regimens [5], and variable clinical response times among patients made follow-up challenging to plan for research coordinators. In addition, the difficulties surrounding patient engagement in survey studies are well known. The barriers to patient survey completion include burnout due to survey length, comprehension difficulties, mode of survey administration, and mistrust in science/research [25]. These challenges should serve to motivate researchers to continue to optimize their methodological approaches to reduce burden for all participants.

Conclusion

Among the 5 patients that completed surveys at baseline and count recovery, study results showed a greater decrease (worsening) in AML-QoL scores for patients receiving induction therapy with the 7+3 regimen compared to Vyxeos following completion of one induction cycle among patients with tAML or AML-MRC. The differences observed between treatment types warrants further investigation to better understand the impact of AML therapies on patient QoL. Additionally, findings from this study illustrate the challenges in conducting real-world, QoL studies among patients with tAML or AML-MRC and should serve as a learning experience for future investigators.

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Disclosures

Deb Profant was an employee of Jazz Pharmaceuticals, Palo Alto, CA at the time of this study.

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Appendices

Appendix 1. Patient Inclusion and Exclusion Criteria

Inclusion

1. Patients who are at least 18 years of age at time of AML diagnosis
2. Pathological diagnosis of AML according to WHO criteria (with at least 20% blasts in the peripheral blood or bone marrow)

Documentation of antecedent hematologic disorder:

- Therapy-related AML (t-AML): Documentation of prior cytotoxic therapy or radiation therapy for an unrelated disease in a discharge summary or pharmacy records or radiation therapy records
- MDSAML: Bone marrow documentation of MDS prior to diagnosis of AML
- CMMoLAML: Bone marrow documentation of Chronic Myelomonocytic Leukemia (CMMoL) prior to diagnosis of AML
- de novoAML with FISH or cytogenetic changes linked to MDS per WHO criteria.

Planned induction treatment with

- 7+3 (100mg/m2/day of cytarabine administered by continuous infusion for 7 days and 60mg/m2 of daunorubicin [or comparable anthracycline] given on days 1, 2 and 3 or institutional 7+3 dosing regimen with cytarabine and anthracycline), OR
- VYXEOS (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2 liposome via intravenous infusion over 90 minutes on days 1, 3, and 5)
- Patients with at least 5th-grade literacy proficiency in English
- Able to adhere to the study visit schedule and complete electronic questionnaires and other protocol requirements.

Exclusion

- Patients with a diagnosis of acute promyelocytic leukemia (APL)
- Patients who received Vyxeos off-label for an indication other than t-AML or AML-MRC
- Patients not receiving Vyxeos or 7+3 therapy for induction therapy.
- Patients receiving additional AML directed therapy (FLT3/IDH/venetoclax)
- Patients with any serious medical condition, laboratory abnormality or psychiatric illness that would prevent obtaining informed consent or completing quality of life surveys.

Appendix 2. Case Report Form to Obtain Patient Information

1. Demographic characteristics

a) Age ____

b) Sex _____

c) Race _____

d) Region _____

e) Marital status _____

2. Clinical characteristics

- Comorbidities
- Myocardial Infarction
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Dementia
- Chronic Pulmonary Disease
- Connective Tissue Disease
- Peptic Ulcer disease
- Liver disease
- Diabetes
- Hemiplegia
- Paraplegia
- Renal Disease
- Hepatitis C
- Celiac Disease
- Lupus
- Rheumatoid Arthritis
- Hashimoto's disease
- Graves' disease

- Psoriasis
- Vasculitis
- Hemolytic Anemia
- Primary Biliary Cholangitis
- HIV
- Sicca syndrome
- Regional enteritis
- Ménière's disease
- Polymyalgia rheumatic
- Addison's disease
- Ulcerative colitis
- Giant cell arteritis
- Pneumonia
- Tuberculosis
- Silicosis
- Asthma
- Emphysema
- Cystic Fibrosis

3. Disease characteristics

Karnofsky performance status at cancer diagnosis

- 100%
- 90%
- 80%
- 70%
- 60%
- 50%
- 40%
- 30%

- 20%
- 10%
- 0

ECOG performance status at cancer diagnosis

- Grade 0
- Grade 1
- Grade 2
- Grade 3
- Grade 4
- Grade 5

Type of AML

- T-AML
- AML with antecedent MRC
- With prior HMA
- Without prior HMA
- AML with antecedent CMML
- De novo AML with MDS karyotype

Prior anthracycline exposure

- Yes
- No

Prior HMA

- Yes
- No

Cytogenetic risk by ELN/NCCN

- Favourable
- Intermediate
- Unfavorable
- Bone Marrow Blasts _____

- WBC at induction _____

4. Treatment Patterns

a) Induction treatment start date (MM/DD/YYYY) _____

b) Induction treatment stop date (MM/DD/YYYY)_____

Type of treatment

- 7+3 (100mg/m2/day of cytarabine administered by continuous infusion for 7 days and 60mg/m2 of daunorubicin [or comparable anthracycline] given on days 1, 2 and 3 or institutional 7+3 dosing regimen with cytarabine and anthracycline
- VYXEOS (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2 liposome via intravenous infusion over 90 minutes on days 1, 3, and 5)

c) Re-induction treatment start date (MM/DD/YYYY) _____

d) Re-induction treatment stop date (MM/DD/YYYY) _____

Type of Treatment

- 7+3 (100mg/m2/day of cytarabine administered by continuous infusion for 7 days and 60mg/m2 of daunorubicin [or comparable anthracycline] given on days 1, 2 and 3 or institutional 7+3 dosing regimen with cytarabine and anthracycline
- VYXEOS (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2 liposome via intravenous infusion over 90 minutes on days 1, 3, and 5)
- Other _____

e) Consolidation treatment start date (MM/DD/YYYY) _____ (repeating measure for each round)

Type of Treatment

- HiDAC
- iDAC
- LoDAC
- Other _____

f) Consolidation treatment stop date (MM/DD/YYYY) _____

g) Salvage therapy start date (MM/DD/YYYY) _____

1) Salvage Regimen _____

h) Salvage therapy stop date (MM/DD/YYYY) _____

1) Date of HSCT (MM/DD/YYYY) _____

5. Responses to induction therapy10

- Complete remission without minimal residual disease (CRMRD)

- Complete remission (CR)
- CR with incomplete hematologic recovery (CRi)
- Morphologic
- Date of response (MM/DD/YYYY) _____

6. Relapse

- Date of disease relapse (MM/DD/YYYY)_____

7. Survival

Status at last follow-up (select all that apply)

- Disease in remission
- Active disease receiving treatment
- Active disease in hospice care
- Active disease not currently receiving treatment
- Death
- Other

Date of last follow-up (MM/DD/YYYY) _____

Appendix 3. Cancer centers contacted for study participation

Holden Cancer Center - University of Iowa	Mayo Clinic Comprehensive Cancer Center - Arizona
Ohio State University Cancer Center	Masonic Cancer Center - University of Minnesota
Dartmouth Cancer Center	University of North Carolina - Chapel Hill
University of Virginia Cancer Center	The University of Kansas Cancer Center
Rutgers Cancer Institute of New Jersey	Novant Health
City of Hope Comprehensive Cancer Center	Loma Linda Medical Center
Moffitt Cancer Center	Tulane University
Roswell Park Comprehensive Cancer Center	Atrium Health
Stephenson Cancer Center	Thomas Jefferson University Hospital
Knight Cancer Institute - Oregon	The University of Cincinnati Cancer Center
University of Wisconsin Carbone Cancer Center	University of Virginia Cancer Center
MD Anderson Cancer Center	Cedars-Sinai Cancer Institute
University of Colorado Cancer Center	Yale Cancer Center
Vanderbilt-Ingram Cancer Center	University of California San Francisco Cancer Center
Henry Ford Cancer Institute	University of Nebraska Medical Center

Appendix 4: Patient recruitment and survey dissemination plan

1. Early identification of adult patient newly diagnosed with AML (t-AML or MDS-related AML) and fit for induction therapy with

7+3 or Vyxeos, to be done by:

a) Health care provider (HCP includes clinical pharmacist, physician, nurse) during initial work up

b) PORC team member with access to EPIC (only applicable to HCI)

2. HCP briefly mentions study to patient and ascertains patient's interest

3. If patient is agreeable to learning more about study, patient allows his/her name and preferred phone number to be provided to Study Coordinator (SC)

a) Preferred phone number may include personal number, friend/family's number, hospital room number

4. SC calls patient at preferred phone number and screens for study eligibility

5. If patient is eligible for study participation, SC performs remote study consent including email address

6. SC sends unique link to QoL survey in Qualtrics for Baseline assessment

a) Baseline defined as from 1 week prior to start of induction treatment and up to day of induction treatment

7. SC verifies that patient has received working link to QoL survey

8. Patient independently completes questionnaire on device available to them, i.e., iPhone, iPad, computer in hospital room

a) SC contacts patient within 24 hours from sending link to QoL survey if patient has not started survey

9. SC follows patient's treatment course and sends subsequent links to the QoL survey according to protocol timeline

- SC verifies nadir, count recovery, etc. with HCP
- SC remits honorarium ($20 gift card) to patient after survey is completed at each time point
- If patient is unable to complete QoL survey at any timepoints or partially completes QoL survey, SC to continue to next timepoints

10. SC maintains Master List of patients on password-protected file saved on site-approved servers behind firewall

- Master List includes demographic data, clinical data, and study data
- Demographic: patient name, preferred phone number, email address
- Clinical data: MRN, confirmation of t-AML or MDS-arising AML, date of induction therapy, date of nadir, date of count recovery, date of intensive chemotherapy, date of post count recovery
- Study data: dates that each link to QoL survey for each time point was sent to patient

11. SC ensures that patient-level data is abstracted at each time point using the CRF

Appendix 5: Study variables

Outcomes Variables

QoL domains from AML-QoL survey

- Physical domain

- Social domain
- Cognitive domain
- Anxiety domain
- Depression domain
- Symptom index
- Taste item
- Bleeding item
- Nausea item
- Fever item
- Bowel item
- Sleep item
- Pain item
- QoL item

QoL domains from EORTC QLQ-C30 survey

- Global Health Status/QoL
- Physical functioning
- Role functioning
- Emotional functioning
- Cognitive functioning
- Social functioning
- Fatigue
- Nausea and vomiting
- Pain
- Dyspnea
- Insomnia
- Appetite loss
- Constipation
- Diarrhoea

- Financial difficulties

Treatment tolerability profiles from PRO-CTCAE survey

Oral

- Difficulty swallowing

Gastrointestinal

- Decreased appetite
- Taste changes
- Nausea
- Vomiting
- Diarrhoea

Cutaneous

- Hair loss

Pain

- General pain

Sleep/wake

- Fatigue
- Insomnia

Mood

- Anxiety
- Discouraged
- Sad

Independent Variables of Interest

- Demographics: age, gender, comorbidities, race, region, marital status
- Disease characteristics: AML diagnosis (t-AML or AML-MRC), Karnofsky performance score, ECOG performance score
- Treatment patterns
- Responses to treatment
- Survival: status at last follow-up