Documenta Haematologica -
Revista Romana de Hematologie | 2024, Vol. 2, Nr. 2

https://doi.org/10.59854/dhrrh.2024.2.2.87

– ORIGINAL PAPERS –

Real-World Treatment Patterns and Clinical Outcomes in Unfit AML Patients: Results of Current Retrospective Study in Romania

Sabina ILUTA[1,2], Angela Smaranda DASCALESCU[3,4]*, Alexandra Elena GHIAUR[5], Ciprian TOMULEASA[1,2], Geanina STINGU[6]

Abstract

Aim: *The incidence of acute myeloid leukemia (AML) increases along with the aging population and its prognosis worsens with increasing age. Limited data is available on the real-world survival, clinical outcomes, and treatment patterns in Romanian AML patients unfit for intensive chemotherapy. Given the rapidly changing AML treatment landscape, this retrospective chart review aimed to understand historical AML treatment pathways, their associated outcomes, and the economic impact.*

Material and methods. *Adult patients across Romania with primary or secondary AML, ineligible for intensive induction chemotherapy, for whom the first-line systemic therapy (FLST) or best supportive care (BSC) was initiated between January 2015 and December 2018 were evaluated. The outcomes assessed included overall survival (OS), progression-free survival (PFS), response rates and healthcare resource utilization (HRU).*

Results*. Of the 98 patients included, 85.7% received FLST and 14.3% received BSC as first-line therapy. The median OS was 10.0 months in those who received a hypomethylating agent as FLST and 3.4 months in the BSC group. Median PFS was 8.0, 6.4, and 3.4 for hypomethylating agents and low-dose cytarabine as FLST, and BSC, respectively. During the first line therapy the best response was stable disease and was achieved in 20.2% of the FLST patients and 14.3% of the BSC patients. HRU was generally numerically higher in patients with FLST as compared to the ones who received BSC as first-line therapy.*

Conclusion. *The survival and outcomes of unfit AML patients in Romania remain poor highlighting the unmet need for effective treatment options in this population.*

Keywords: *acute myeloid leukemia, unfit patients, hypomethylating agents, best supportive care, real-world*

[1] Medfuture Research Center for Advanced Medicine / Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[2]Department of Hematology, Ion Chiricuta Clinical Cancer Center, Cluj-Napoca, Romania

[3]University of Medicine and Pharmacy Grigore T. Popa, Iasi, Romania

[4]Department of Hematology, Regional Oncology Institute, Iasi, Romania

[5]Department of Hematology, Fundeni Clinical Institute, Bucharest, Romania

[6]Abbvie, Bucharest, Romania

Corresponding author:
*** Angela Smaranda DASCALESCU,** MD, PhD, Department of Hematology, Regional Oncology Institute, 2-4 General Henri Mathias Berthelot Str., Iasi, Romania
email: angdascalescu@yahoo.com

Introduction

Acute myeloid leukemia (AML) is the most frequent type of leukemia in adults. Although it is a rare type of cancer, its incidence rates have increased over time, from an age-adjusted incidence of 3.43/100,000 person-years in the '70s in the US to more than 4.2/100,000 person-years from 2010 onward (1). A similar increase in the incidence rates has been also reported in Europe, Canada, and Australia (2)(3)(4). With regards to its distribution across age and sex, AML mainly affects the elderly, with sharply increasing incidence after the age of 60 and with higher rates in men than in women (5).

Despite recent advances in therapeutics and supportive care which have improved the outcomes of patients with AML, the 5-year survival rates remain low, ranging between 19% and 29% (6)(7)(8)). However, this improvement is generally limited to patients younger than 65 years (9) and little progress has been observed in the elderly; the mortality rates registered minimal changes in the past decades and long-term survival is still poor (9)(10). Standard AML therapy includes intensive induction and consolidation chemotherapy, followed by post-remission allogeneic hematopoietic stem cell transplantation in high-risk eligible patients (10). Since 2013, criteria of unfitness to intensive and non-intensive chemotherapy in AML patients were proposed (11) and proved to be good predictors of early mortality after intensive chemotherapy and survival (11)(12). In particular, older patients are more likely to not tolerate intensive chemotherapy due to comorbidities or frailty and experience treatment-related mortality (10). In real-life practice only a minority of elderly with AML are treated with intensive chemotherapy (13).

The treatment of elderly patients with AML considered unfit for intensive induction chemotherapy represents a great challenge in clinical practice. Few treatment options have been available until very recently, and these included the hypomethylating agents (HMA) azacitidine or decitabine, low-dose cytarabine (LDCA), targeted therapy, and best supportive care (BSC) with hydroxyurea or transfusion support; the median overall survival (OS) with these therapies is usually below 1 year (14)(15)(16). Based on the results of the VIALE-A clinical trial which showed improved survival on venetoclax plus azacitidine compared to azacitidine alone (17), current guidelines recommend venetoclax plus azacitidine as a preferred treatment option for AML patients unfit for intensive chemotherapy (18). Also, venetoclax plus LDCA represents a treatment option for patients who cannot receive HMA and ivosidenib is currently recommended in AML patients with IDH1 mutation unfit for intensive chemotherapy (18).

The number of new AML cases increases each year along with the aging population. With the increasing incidence and rising cost of treatment, there is a need to understand AML treatment pathways, their associated treatment outcomes, and the economic impact in different health care systems.

Given the paucity of leukemia or treatment registries in Romania, limited data is published about real-world survival, clinical outcomes, treatment patterns, and healthcare resource utilization (HRU) in AML patients unfit for intensive chemotherapy. Therefore, Romania participated in a multinational study - the Real-World Treatment Patterns and Clinical Outcomes in Unfit AML Patients Receiving First Line Systemic Treatment or Best Supportive Care (CURRENT) study - with an overarching goal to understand the real-life treatment patterns and clinical outcomes in unfit AML patients receiving first-line systemic treatment or BSC across different geographies (19)(20). Here we present the results in the sub-set of patients from Romania.

Material and methods

Study design, patients, and data collection

CURRENT was a real-world non-interventional, retrospective chart review study of patients diagnosed with primary or secondary AML and deemed ineligible for intensive chemotherapy based on treating physician's assessment of age, performance status, comorbidities, regional guidelines, or institutional practice or all of these (21). Patients' charts and/or site documentation were checked by study investigators to verify eligibility criteria. Eligible patients were required to have first-line therapy initiated between January 2015 and December 2018. Patients were followed until the last recorded contact or date of death, whichever was applicable at the time of data collection. The study was conducted in 112 medical centers from 22 countries, of which 3 were in Romania (19) (20).

In Romania, the study protocol was approved by the National Ethics Committee for Medicine and Medical Devices with a waiver of the informed consent in patients alive at the time of data collection.

The study included all adult patients (age ≥18 years) diagnosed with primary or secondary AML, ineligible for intensive chemotherapy as per their treating physician's assessment, with previous first-line systemic therapy (FLST) including low-intensity chemotherapy and

targeted therapy or BSC and who underwent ≥2 visits in addition to the visit related to the start of FLST or BSC. Patients without a confirmed AML diagnosis, those with acute promyelocytic leukemia, and those who received the first-line AML therapy within a clinical study were excluded (19) (20). In sites with a high number of eligible patients identified, a random sampling method was used to select patients for study inclusion: the total number of eligible patients was divided by the maximum number allowed to enroll to determine the selection factor (i.e., every 3rd or 4th patient) (20). However, each study center was allowed to enroll between 5 and 35 patients, with the maximum number defined locally.

The following data were collected from eligible patients' medical charts and site documentation: age at AML diagnosis, gender, baseline clinicopathologic characteristics, cytogenetic and molecular profiles, treatment patterns, and supportive care. Baseline clinicopathologic characteristics extracted were AML WHO classification, Eastern Cooperative Oncology Group (ECOG), primary or secondary AML, comorbidities, and risk stratification (favorable, intermediate, adverse). To describe treatment patterns and supportive care, the following information was collected: type and duration of AML treatment (first and subsequent lines of therapy), number of treatment cycles received, the reason for treatment discontinuation, and supportive care medication prescribed during the study observation period.

Study endpoints

The primary endpoint was the OS defined as the time from the date of a confirmed diagnosis of AML (index date) to death of any cause, as documented in the medical chart. Patients alive were censored on the study end date or on the last contact date available in the dataset, whichever occurred first. The cut-off for study end was 31st of March 2020 (19). Secondary endpoints included progression-free survival (PFS), time to treatment failure (TTF), HRU, and response rates per physician assessment. PFS was calculated as the time from the date of a confirmed diagnosis of AML to the date of physician-assessed disease progression or death due to any cause. TTF was measured as the time from the start of systemic therapy, targeted therapy, or BSC until discontinuation of the treatment due to any reason. HRU was assessed by receipt of transfusions (red blood cell and/or platelet), hospital admissions (including days spent in an intensive care unit), the number of outpatient consultations, supportive care received (including growth factors), antibiotics use and the use of other medications from the initiation of FLST or BSC until treatment discontinuation. The rates of complete remission (CR), CR with incomplete hematologic recovery (CRi), partial remission (PR), and treatment failure were captured as per the physician's assessment.

Statistical analysis

Due to the descriptive nature of the study, no formal sample size calculation was performed, and a global target sample of 1600 patients with AML was set (19). At global study level, this sample size was considered sufficient to allow reasonably precise estimates (the width of a two-sided 95% confidence interval for proportion-based estimates were within ±2.8% with n=1200, using normal approximation for binomial distribution) Results were analyzed for the full analysis population and in subgroups of patients with FLST or BSC. The results were also presented by specific geographies (n 50 per country or area was required; widths at most ±13.9% with n=50) (19) (20).

Data were summarized using descriptive statistics, and presented as means, standard deviations, medians, and quartiles for continuous variables and numbers and percentages for categorical variables. For time to event analyses (OS, PFS, TTF), the Kaplan-Meier method was used to estimate proportions and median times.

Results

Patient demographics and clinical characteristics

Of the 1762 patients with AML included globally in the CURRENT study, 98 were from Romania. Of these, 84 (85.7%) received FLST, consisting of HMA monotherapy (77.4%), decitabine (72.6%) and azacitidine (4.8%), and LDAC (25.0%) and were included in the FLST group, whereas 14 (14.3%) patients received BSC as first-line therapy (included in the BSC group) (Table 1).

Baseline characteristics were generally similar between the FLTS and BSC cohorts, although gender, age and ECOG distribution differed across groups (56% men in FLST vs. 35.7% in BSC, mean age 71.3 years in FLTS vs. 80.6 years in BSC and 63.3% ECOG≥2 in FLST vs. 42.9% in BSC, with no ECOG 0-1 in the BSC group). In both groups, the most frequent form of AML at diagnosis according to WHO classification was AML not otherwise specified. In the FLTS group, the cytogenetic risk was favorable in 9.5% of patients, intermediate in 27.4% and adverse in 6% of patients, although it was listed as unknown in most patients (57.1%). In the BSC group most patients (85.7%) had an unknown cytogenetic analysis risk (Table 1).

Table 1. *Patient demographic and clinical characteristics*

	FLST N=84	BSC N=14	Full analysis population N=98
Men, n (%)	47 (56.0%)	5 (35.7%)	52 (53.1%)
Age, years	71.3±5.39	80.6±3.92	72.7±6.12
Age at diagnosis ≤75 years, n (%)	60 (71.4%)	1 (7.1%)	61 (62.2%)
Secondary AML, n (%)	21 (25.0%)	3 (21.4%)	24 (24.5%)
Unknown	2 (2.4%)	1 (7.1%)	3 (3.1%)
ECOG performance status, n (%)			
0-1	7 (8.3%)	0	7 (7.1%)
≥2	62 (63.3%)	6 (42.9%)	54 (55.1%)
Unknown	29 (34.5%)	8 (57.1%)	37 (37.8)
Type of AML at diagnosis (WHO), n (%)			
AML with recurrent genetic abnormalities[a]	4 (4.8%)	0	4 (4.1%)
AML with mutated NPM1	4 (100%)	0	4 (100.0%)
AML with myelodysplasia-related changes	16 (19.0%)	2 (14.3%)	18 (18.4%)
Therapy-related myeloid neoplasms	1 (1.2%)	0	1 (1.0%)
AML not otherwise specified[a]	30 (35.7%)	3 (21.4%)	33 (33.7%)
AML with minimal differentiation	5 (16.7%)	1 (33.3%)	6 (18.2%)
AML without maturation	1 (3.3%)	0	1 (3.0%)
AML with maturation	6 (20.0%)	0	6 (18.2%)
Acute myelomonocytic leukemia	14 (46.7%)	1 (33.3%)	15 (45.5%)
Acute monoblastic/monocytic leukemia	2 (6.7%)	0	2 (6.1%)
Pure erythroid leukemia	1 (3.3%)	0	1 (3.0%)
Acute megakaryoblastic leukemia	1 (3.3%)	1 (33.3%)	2 (6.1%)
Unknown	33 (39.3%)	9 (64.3%)	42 (42.9%)
Molecular abnormalities, n (%)			
Any mutation[a]	11 (13.1%)	0	11 (11.2%)
TP53	1 (9.1%)	0	1 (9.1%)
FLT3	1 (9.1%)	0	1 (9.1%)
FLT3^{ITD}	4 (36.4%)	0	4 (36.4%)
JAK2	1 (9.1%)	0	1 (9.1%)
NPM1	5 (45.5%)	0	5 (45.5%)
Other	1 (9.1%)	0	1 (9.1%)
None	40 (47.6%)	3 (21.4%)	43 (43.9%)
Unknown	33 (39.3%)	11 (78.6%)	44 (44.9%)
Cytogenetic risk, n (%)			
Favorable	8 (9.5%)	0	8 (8.2%)
Intermediate	23 (27.4%)	1 (7.1%)	24 (24.5%)
Adverse	5 (6.0%)	1 (7.1%)	6 (6.1%)
Unknown	48 (57.1%)	12 (85.7%)	60 (61.2%)
Comorbidities, n (%)			
Yes	76 (90.4%)	13 (92.9%)	89 (90.8%)
Myocardial infarction	6 (7.1%)	1 (7.1%)	7 (7.1)
Angina / coronary artery disease	11 (13.1%)	2 (14.3%)	13 (13.3)
Congestive heart failure	17 (20.2%)	5 (35.7%)	22 (22.4)
Arrhythmias	18 (21.4%)	8 (57.1%)	26 (26.5)
Restrictive lung disease or COPD	8 (9.5%)	1 (7.1%)	9 (9.2)
Liver Cirrhosis	1 (1.2%)	0	1 (1.0)
Renal failure or CKD stage 3, 4 or 5	3 (3.6%)	0	3 (3.1)
Unknown	3 (3.6%)	1 (7.1%)	4 (4.1%)
First-line treatment received			
Systemic therapy			
HMA	65 (77.4%)		84 (85.7%)
Azacitidine	4 (4.8%)		
Decitabine	61 (72.6%)		
LDAC	21 (25.0%)		
Other	1 (1.2%)		
BSC only			
Transfusions as needed		14 (100.0%)	14 (14.3%)
Pain relief		9 (64.3%)	
Nutritional support		8 (57.1%)	

Infection management		11 (78.6%)
Other		1 (7.1%)
Number of cycles received	6.0±7.52	
Duration of 1st line treatment or BSC, days	32.0 (14.0; 107.0)	110.5 (78.0; 176.0)
Reason for 1st line therapy or BSC discontinuation		
Disease progression	29 (38.2%)	1 (7.1%)
Toxicity	7 (9.2%)	0
Decline in performance status	17 (22.4%)	2 (14.3%)
Death	29 (38.2%)	10 (71.4%)
Patient Preference	5 (6.6%)	1 (7.1%)
Physician Preference	8 (10.5%)	0
Other	3 (3.9%)	0
Unknown	4 (5.3%)	3 (21.4%)
1st line treatment failure, n (%)	71 (84.5%)	11 (78.6%)
Time from 1st line treatment or BSC initiation to treatment failure, days	30.0 (10.0; 94.0)	109.0 (78.0; 176.0)

[a]*Number used as denominator for the following sub-categories.*
AML, acute myeloid leukemia; BSC, best supportive care; FLST, first line systemic therapy; FLT3, FMS-like tyrosine kinase-3; HMA, hypomethylating agent; JAK2, Janus-associated kinase 2; LDAC, low-dose cytarabine; NPM1, nucleophosmin 1; N/n (%), number (%); TP53, tumor protein 53; WHO, World Health Organization Category 'Other' includes cytarabine, aclarubicin, G-CSF regimen, enocitabine, combination of therapies, venetoclax, and other.

OS and response outcomes to the first line of therapy

At the time of data collection, 78 (79.6%) patients were deceased, with a mean time from diagnosis to death of 7.2 months. By study groups, at the time of data collection, 76.2% of the patients in FLST and 100% of patients in the BSC groups were deceased. Median OS (95% CI) at the time of data collection was 8.6 (5.6: 11.1) months, significantly lower in the BSC group than in patients who received an HMA as FLST (3.4 [1.5; 5.8] months vs.10.0 [6.0; 14.6] months: p<0.001) (Figure 1).

The most frequent cause of death was disease progression, infection, and other comorbid conditions in the FLST group and disease progression in the BSC group.

Median PFS (95% CI) was 6.0 (4.1: 8.3) months, being longer in those who received an HMA as FLST than in those who received another type of therapies (8.0 [4.7; 10.1] months in those who received HMA vs. 6.4 [2.9; 10.4] months in LDCA vs. 3.4 [1.5; 5.8] months in BSC group; p=0.009). Median TTF (95% CI) from diagnosis from diagnosis of AML was longer in the BSC group (3.6 [1.4; 5.8] months) as compared to the systemic therapy group (2.1 [1.2; 3.5] months in those who received HMAs, 0.4 [0.3; 0.7] months in those who received LDCA and 1.0 [0.9; 1.1] month in those who received other systemic therapies; p<0.001). During the first line therapy most patients in the FLST group achieved stable disease (20.2%), PR (9.5%), and PD in 9.5% of the patients, and CR and CRi in 10.7% of the patients, with a median time from the start of treatment to the best response of 110.5 [60.0; 192.00] days. In FLTS group the median time from start of treatment to best response was 3.7 (0.9-23.2) months, the median duration of CR/CRi was 15 (4.2-15.6) months, and the median time from start of treatment to disease progression was 5.5 (0.7-19.6) months. The best overall response in the BSC group was stable disease in 14.3% of the patients (Table 2)

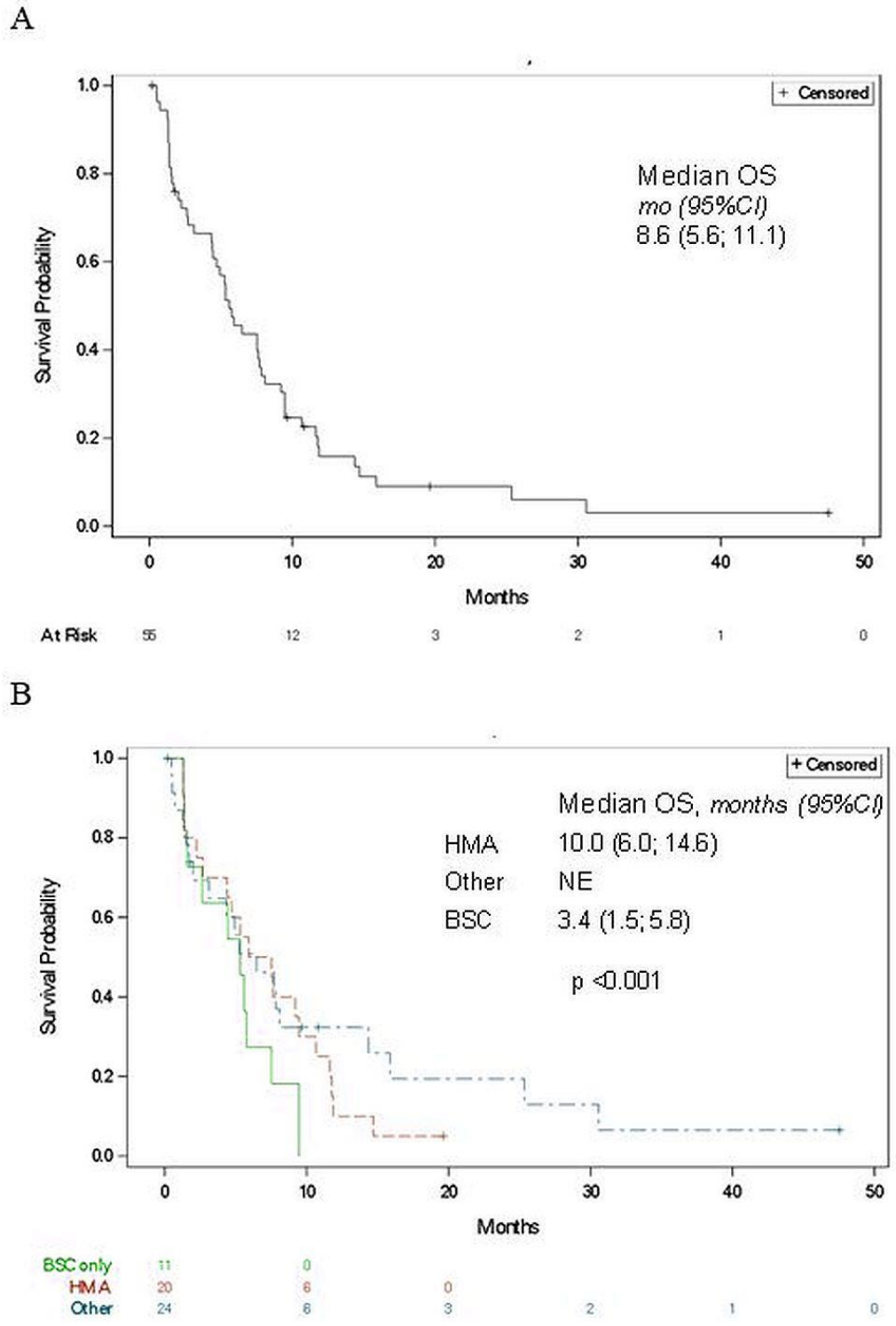

Figure 1. *Kaplan-Meier survival curves for (A) the full analysis population and (B) according to the type of first line of treatment)*

BSC, best supportive care; HMA, hypomethylating agent; OS, overall survival
Category 'Other' includes cytarabine, aclarubicin, G-CSF regimen, enocitabine, combination of therapies, venetoclax, and other.

Table 2. *Outcomes of the therapy and healthcare resource utilization during the first line therapy by treatment type*

	FLST N=84	**BSC N=14**
Outcomes of therapy		
Best overall response of the first line of therapy, n (%)		
CR	7 (8.3%)	0
CRi	2 (2.4%)	0
PR	8 (9.5%)	0
SD	17 (20.2%)	2 (14.3%)
PD	8 (9.5%)	1 (7.1%)
Unknown	42 (50.0%)	11 (78.6%)
Time from start of treatment to best response, days[a]	110.5 (60.0; 192.00)	-
Duration of CR/CRi, days[a]	449.0 (127.0; 468.00)	-
Time from start of treatment to disease progression, days[a]	166.0 (71.0; 305.50)	-
Healthcare resource utilization		
Patients hospitalized, n (%)	84 (100.0%)	14 (100.0%)
Number of hospitalizations[a]	12.0 (5.0; 20.0)	3.0 (2.0; 5.0)
Reason for hospitalization, n (%)		
Progression/Relapse-related	43 (6.6%)	6 (14.3%)
Infection-related	201 (30.9%)	24 (57.1%)
Transfusion-related	316 (48.5%)	40 (95.2%)
Treatment administration-related	492 (75.6%)	0
Other AML-related event	51 (7.8%)	4 (9.5%)
Other	62 (9.5%)	3 (7.1%)
Unknown	1 (0.2%)	0
Number of days hospitalized	9.6±8.29	8.4±5.82
Number of days in ICU	0.2±1.42	0.2±1.39
Patients with outpatient consultation, n (%)	50 (59.5%)	12 (85.7%)
Number of outpatient visits	11.2±17.04	10.5±12.37
Patients with RBC/platelet transfusions	49 (58.3%)	12 (85.7%)
Number of RBC transfusions[a]	13.0 (3.0; 24.00)	10.0 (7.0; 18.00)
Growth factors use, n (%)	27 (32.1%)	3 (21.4%)
Reason for use, n (%)		
Prophylaxis	27 (100.0%)	3 (100.0%)
Route of administration, n (%)		
Parenteral	25 (92.6%)	3 (100.0%)
Unknown	2 (7.4%)	0
Number of days on growth factors	31.8±26.81	7.5±6.36
Antibiotics and antivirals use, n (%)	81 (96.4%)	14 (100.0%)
Reason for use, n (%)		
Prophylaxis	73 (90.1%)	11 (78.6%)
Curative	70 (86.4%)	12 (85.7%)
Route of administration, n (%)		
Oral	66 (81.5%)	6 (42.9%)
Parenteral	71 (87.7%)	13 (92.9%)
Unknown	1 (1.2%)	0
Number of days on antibiotic/antiviral	111.4±157.79	15.2±10.69
Antifungals use, n (%)	52 (61.9%)	11 (78.6%)
Reason for use, n (%)		
Prophylaxis	48 (92.3%)	10 (90.9%)
Curative	22 (42.3%)	1 (9.1%)
Route of administration, n (%)		
Oral	42 (80.8%)	5 (45.5%)
Parenteral	37 (71.2%)	9 (81.8%)
Number of days on antifungals	81.9±129.5	15.2±13.6

[a]*Results are presented as median (quartile 1; quartile 3).*
AML, acute myeloid leukemia; BSC, best supportive care; CI, confidence interval; CR, complete response; CRi, complete response with incomplete hematologic recovery; FLST, first line systemic therapy; ICU; intensive care unit; N/n (%), number (percentage); PR, partial remission; SD, stable disease; PD, progressive disease; RBC, red blood cells

Treatment patterns

The time from diagnosis to initiation of first-line therapy was 17.7±31.69 days. In the FLST group, the mean number of cycles received during the first-line therapy was 6.0±7.5 and the most frequent type of therapy was HMA (azacitidine or decitabine administered in 77.4% of the patients). In the BSC group, the most frequent treatments used in first line were transfusions and medication for infection management and pain relief (Table 1). 27 patients received a second-line therapy (63.0% systemic treatment and 37.0% BSC) and 6 patients a third-line therapy (50.0% systemic treatment and 50.0% BSC) (Supplementary Tables 1 and 2). The change in treatment patterns over the lines of therapy is depicted in Figure 2.

Supplementary table 1. *Overview of the second line of therapy*

	FLST N=17	**BSC** N=10	**Full analysis population** N=27
2nd line treatment received, n (%)			
Systemic therapy			17 (63.0%)
HMA	6 (35.3%)		
Azacytidine	2 (11.8%)		
Decitabine	4 (23.5%)		
LDAC	8 (47.1%)		
Other	3 (17.6%)		
BSC only			10 (37.0%)
Transfusions as needed		10 (100.0%)	
Pain relief		2 (20.0%)	
Nutritional support		3 (30.0%)	
Infection management		8 (80.0%)	
Other		1 (10.0%)	
Time from diagnosis to initiation of 2nd line treatment, days			148.0 (60.0; 285.0)
Number of cycles	2.6±2.60		
Duration of 2nd line treatment, days	10.0 (5.5; 43.5)	175.0 (61.0; 313.0)	
Reason for 2nd line therapy discontinuation, n (%)	7 (43.8%)	3 (37.5%)	
Disease progression	1 (6.3%)	3 (37.5%)	
Decline in performance status	10 (62.5%)	8 (100.0%)	
Death	2 (12.5%)	0	
Physician Preference			
2nd line treatment failure, n (%)	16 (94.1%)	8 (80.0%)	
Time from 2nd line therapy initiation to treatment failure, days	10.0 (5.5; 43.5)	175.0 (61.0; 313.00)	

BSC, best supportive care; FLST, first line systemic therapy; HMA, hypomethylating agent; LDAC, low-dose cytarabine; N/n (%), number (%)

Supplementary table 2. *Overview of the third line of therapy*

	FLST **N=3**	**BSC** **N=3**	**Full analysis population** **N=6**
3rd line treatment received, n (%)			
Systemic therapy			3 (50.0%)
HMA	2 (66.6%)		
Azacytidine	1 (33.3%)		
Decitabine	1 (33.3%)		
LDAC	1 (33.3%)		
BSC only			3 (50.0%)
Transfusions as needed		3 (100.0%)	
Pain relief		1 (33.3%)	
Infection management		1 (33.3%)	
Other		2 (66.7%)	
Time from diagnosis to initiation of 3rd line treatment, days			267.0 (35.0; 460.0)
Number of cycles	5.3±2.08		
Duration of 3rd line treatment, days	30.0 (15.0; 42.0)	157.5 (62.0; 253.0)	
Reason for 3rd line therapy discontinuation, n (%)			
Disease progression	1 (33.3%)	0	
Toxicity	1 (33.3%)	0	
Death	2 (66.7%)	3 (100%)	
Unknown	1 (33.3%)	0	
3rd line treatment failure, n (%)	2 (66.7%)	3 (100.0%)	
Time from 3rd line therapy initiation to treatment failure, days	28.5 (15.0; 42.00)	157.5 (62.0; 253.0)	

BSC, best supportive care; FLST, first line systemic therapy; HMA, hypomethylating agent; LDAC, low-dose cytarabine; N/n (%), number (%)

Healthcare resource utilization

HRU was generally numerically higher in patients in the FLST group as compared to the BSC group. The number of episodes of hospitalization, number of days hospitalized, number of outpatient visits, percentage of patients who used growth factors, and number of days on growth factor or on antibiotic/antiviral medication were higher in the FLST group than in the BSC group. The percentage of patients with outpatient consultations, transfusions, antibiotic/antiviral medication, and antifungals was higher in the BSC group than in the FLST group (Table 2).

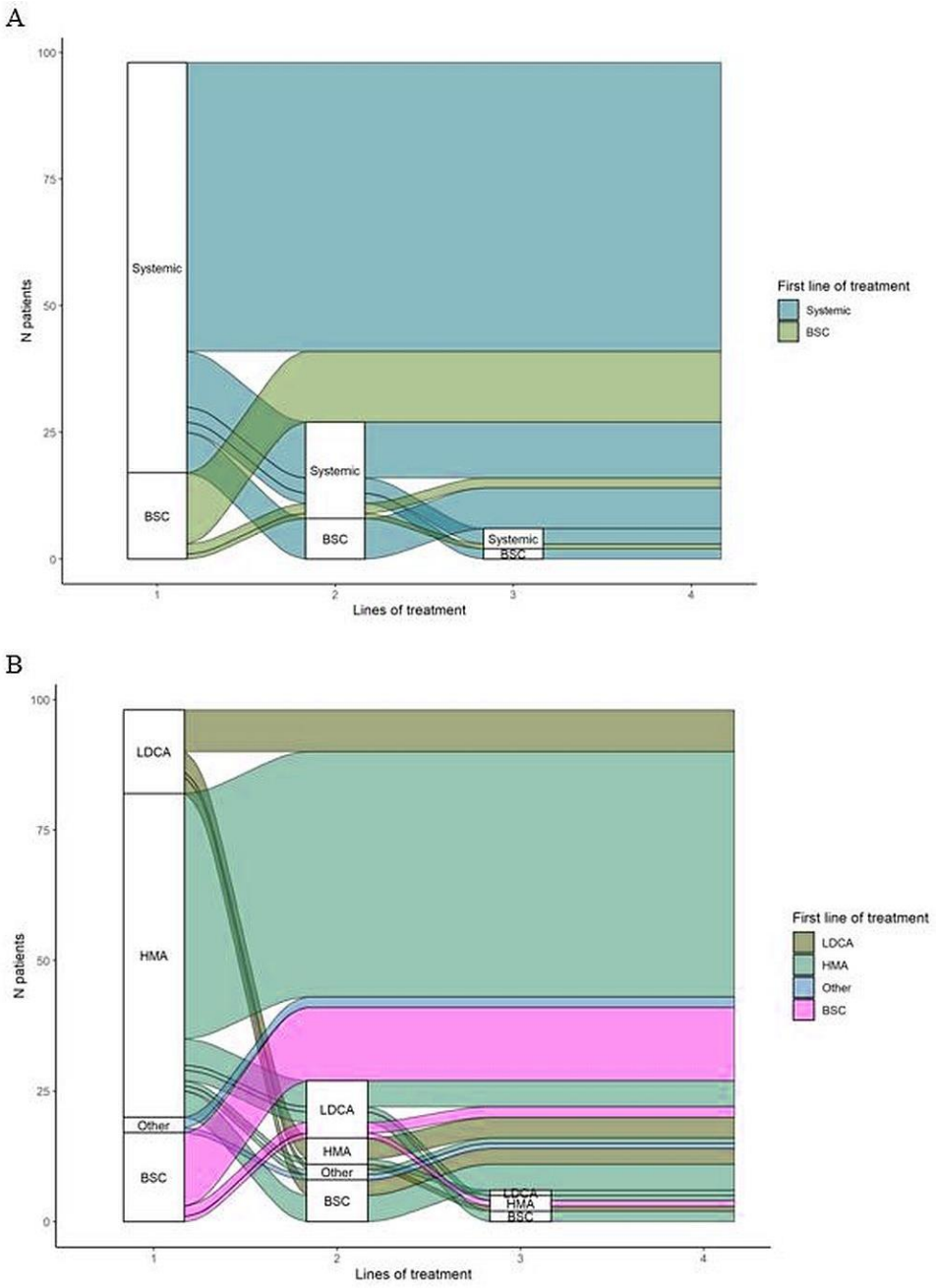

Figure 2. *Alluvial plots showing the change in treatment patterns in Romanian patients over treatment lines for systemic vs. BSC (A) and detailed for systemic therapy (B)*

BSC, best supportive care; HMA, hypomethylating agent; LDAC, low-dose cytarabine; OS, overall survival

Category 'Other' includes cytarabine, aclarubicin, G-CSF regimen, enocitabine, combination of therapies, venetoclax, and other

Discussion

This country analysis from the CURRENT study provided a detailed real-world insight into the treatment patterns, clinical outcomes including survival, clinicopathologic characteristics, and HRU of AML patients unfit to receive intensive chemotherapy in Romania. In our dataset, the clinical outcomes of patients remained unsatisfactory with a median OS of 8.6 months for all study population,

irrespective of treatment options. HMAs (azacitidine or decitabine) use as FLST were common and associated with a significant improvement of survival as compared to BSC (10.0 months vs. 3.4 months). Improved response outcomes to first-line therapy (CR, CRi, or PR) were achieved only in patients on FLST, while the best response achieved by BSC patients was stable disease.

These results are consistent with global CURRENT results (19) and other real-world reports in AML patients (22) (23). In the global CURRENT study (19), the median OS from diagnosis was 6.2 months (95%CI: 5.7; 7.0) within the entire study population. OS was longer in patients receiving FLST compared to patients receiving BSC in the first line: 9.9, 7.9, and 5.4 months for patients who received HMAs, LDAC, and other systemic therapies, respectively, and 2.5 months for patients who received BSC only. Similar median OSs of 11.6 months in patients with a favorable cytogenetic profile and 7.9 months in patients with an adverse cytogenetic profile treated with decitabine were reported in an analysis of real-life pooled data from 3 observational studies enrolling 306 AML patients unfit for intensive chemotherapy (22). In this analysis, 23.2% of patients achieved CR, and when patients achieving a hematologic improvement were included, the CR rate increased to 48.4% (22). The real-world treatment patterns in patients with AML enrolled in the CURRENT trial from Japan included almost 200 patients and reported similar survival and HRU results, despite an increased availability of the genetic and molecular biology data (24). These rather surprisingly similar clinical results in disease outcomes in two very different patient cohorts emphasize the need for an optimized strategy in the challenging population of AML patients ineligible for intensive therapy.

As in other previous real-world studies (19) (23), the analysis of this dataset has also confirmed the common use of systemic therapy as first-line treatment and the preference for HMA in patients considered unfit for intensive chemotherapy. However, in the Romanian AML patients,14.3% received only supportive therapy as first-line therapy despite the availability of regimens that showed improved outcomes. Intensive induction therapy is rarely recommended in the elderly and usually less intensive therapies are used. Worldwide, the use of BSC only is still high among patients >70 years of age accounting in some geographical regions for up to 61% of the patients (25)(26). In the elderly, therapy is chosen based on patient- and disease-specific factors, such as age, presence of unfavourable cytogenetic abnormalities, molecular abnormalities, and presence of secondary AML (27). Additionally, the presence of significant comorbidities and a worse performance status usually render patients unfit for systemic chemotherapy (27). In the Romanian dataset, systemic therapy was more frequently recommended in relatively younger patients (mean age 71 years), who had more frequently an ECOG performance status ≥2, and a favourable or intermediate cytogenetic risk. In a recent US study evaluating 3068 patients aged >60 years with newly diagnosed AML, receiving therapy was associated with younger age (<80 years) and fewer comorbidities (28). Similar data were reported in a Korean cohort, where receiving BSC only was more frequently in patients aged >70 years with a Charlson Comorbidity index ≥2 as compared to those receiving chemotherapy (23).

Cytogenetic and molecular profiles have been identified as prognostic factors for patients with AML (10). Current guidelines recommend cytogenetic and molecular testing as part of the initial assessment for risk stratification and to inform the treatment decision-making (18). Using biomarkers to determine drug sensitivity and prognostic profiles becomes even more important in the era of personalized medicine (29). Despite the important advances in the genetic field, the results of the country analysis show that most Romanian patients included in the CURRENT study had an unknown cytogenetic profile and molecular abnormalities and the proportion was higher in the BSC group as compared to the FLST group (85.7% and 78.6%, respectively). These figures are higher compared to the global CURRENT study (36% and 54% of the BSC group and 28.5% and 44.3% of the FLST group) (19) and reflect the disparities in haemato-oncology care, with limited access to cytogenetic and molecular testing in Romania.

HRU was another aspect analyzed in the CURRENT study. In the Romanian sample, at least one hospitalization was reported for all patients irrespective of the first-line therapy, with a median number of hospital admissions / patient of 12.0 in the FLST group and 3.0 in the BSC group. These figures were higher as compared to other real-world reports in AML patients. In the global CURRENT cohort, 82.0 to 93.0% of the FLST group and 83.0% of the BSC group were hospitalized and the median number of hospitalizations was 4.0-6.0 and 2.0, respectively in these groups (20). In another retrospective analysis of AML patients ineligible for intensive chemotherapy attending US oncology clinics, the hospitalization rates ranged between 79.9% and 83.7% according to the type of HMA used (30). The difference observed between our cohort and the other reports is

probably multi-factorial, residing in clinical characteristics of patients, socio-economic support, and a peculiarity of the healthcare financing model of these patients in Romania. The prevalence of comorbidities, particularly cardiovascular ones, and the incidence of infections seem higher in Romanian patients with AML as compared to data from more developed countries (31)(32)(33)(34).

This real-world analysis has limitations. The retrospective design of the study, relying entirely on information already available in medical charts for data collection is an important limitation. This approach is generally prone to missing data, including information on diagnosis or outcomes of treatment or last vital status or the lack of data on cytogenetics and molecular markers for most patients. Sampling bias during the site and patient recruitment are other limitations, although the consent waivers obtained from the Ethics Committees. Additionally, in sites with higher patients' volume, not all patients identified could be enrolled and a random sampling method was used (20). To our knowledge, the CURRENT study is the first attempt to describe the AML treatment pathways in unfit patients from Romania; however, there is no official, comprehensive, functional leukemia registry to allow for comparisons of these data with other national reports. The participating centers from Romania are national and regional institutes involved in the management of haemato-oncological patients, covering the main geographical regions, and considered most representative. As not all types of practices across the country were included in the study, the generalizability of results is limited. Due to low sample sizes and descriptive study design, without formal power for specific statistical comparisons at country level, the specific survival sub-analyses should be interpreted carefully. Despite these methodological constraints, these findings provide relevant insights for our medical community and will serve as basis for further research at local level to confirm these results and inform on the impact of newer treatment options on patient's outcomes.

Conclusion

The CURRENT study improved understanding of historical AML treatment pathways in Romania, their associated treatment outcomes, and economic impact, as the incidence increases each year and costs of treatment are rising. The survival and outcomes of unfit patients with AML remain poor, highlighting the unmet need for effective treatment options in this population.

Funding

This study was funded by AbbVie.

Acknowledgments

Medical writing support was provided by Adriana Rusu (MD, PhD), MedInteractiv (Bucharest, Romania) on behalf of AbbVie. AbbVie participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

Author contributions

All authors had access to relevant data, and participated in the analysis and interpretation of data, writing, review, and approval of the manuscript and accept to be accountable for the content of the manuscript. SI, ASD, AEG, and CT contributed to data acquisition.

Conflicts of interest

SI declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ASD received honoraria from Bristol-Myers Squibb, Pfizer, Novartis, Janssen, Roche, AstraZeneca, Accord, and AbbVie.

AEG received honoraria from Pfizer, Novartis, Janssen, AstraZeneca.

CT received honoraria from Bristol-Myers Squibb, Pfizer, Novartis, Janssen, and AbbVie.

GS is an employee of AbbVie and may hold stock or options.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M et al (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, based on November 2018 SEER data submission, posted to the SEER web site, April 2019, accessed Mar 08, 2024 (https://seer.cancer.gov/csr/1975_2016/)

2. Gangatharan SA, Grove CS, P'ng S, O'Reilly J, Joske D, Leahy MF, Threlfall T, Wright MP. Acute myeloid leukaemia in Western Australia 1991-2005: a retrospective population-based study of 898 patients regarding epidemiology, cytogenetics, treatment and outcome. Intern Med J. 2013 Aug;43(8):903-11. doi: 10.1111/imj.12169. PMID: 23611681.

3. Shysh AC, Nguyen LT, Guo M, Vaska M, Naugler C, Rashid-Kolvear F. The incidence of acute myeloid leukemia in Calgary, Alberta, Canada: a retrospective cohort study. BMC Public Health. 2017 Aug 3;18(1):94. doi: 10.1186/s12889-017-4644-6. Erratum in: BMC Public Health. 2017 Sep 22;17 (1):736. PMID: 28774275; PMCID: PMC5543578.

4. Roman E, Smith A, Appleton S, Crouch S, Kelly R, Kinsey S, Cargo C, Patmore R. Myeloid malignancies in the real-world: Occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004-15. Cancer Epidemiol. 2016 Jun;42:186-98. doi: 10.1016/j.canep.2016.03.011. Epub 2016 Apr 16. PMID: 27090942; PMCID: PMC4911595.

5. Juliusson, G., Abrahamsson, J., Lazarevic, V., Antunovic, P., Derolf, Å., Garelius, H., et al. (2017). Prevalence and characteristics of survivors from acute myeloid leukemia in Sweden. Leukemia. 31, 728-731. doi: 10.1038/leu.2016.312.

6. Cancer stat facts: leukemia – acute myeloid leukemia. National Cancer Institute, accessed March 08, 2024 (https://seer.cancer.gov/statfacts/html/amyl.html)

7. Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol. 2011 Nov 20;29(33):4417-23. doi: 10.1200/JCO.2011.35.7525. Epub 2011 Oct 3. PMID: 21969499; PMCID: PMC3221524.

8. Visser O, Trama A, Maynadié M, Stiller C, Marcos-Gragera R, De Angelis R, et al; RARECARE Working Group. Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer. 2012 Nov;48(17):3257-66. doi: 10.1016/j.ejca.2012.05.024. Epub 2012 Jul 4. PMID: 22770878.

9. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. Blood Rev. 2019 Jul;36:70-87. doi: 10.1016/j.blre.2019.04.005. Epub 2019 Apr 29. PMID: 31101526.

10. Heuser M, Ofran Y, Boissel N, Brunet Mauri S, Craddock C, Janssen J, et al; ESMO Guidelines Committee. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Jun;31(6):697-712. doi: 10.1016/j.annonc.2020.02.018. Epub 2020 Mar 17. Erratum in: Ann Oncol. 2021 Jun;32(6):821. PMID: 32171751.

11. Ferrara F, Barosi G, Venditti A, Angelucci E, Gobbi M, Pane F, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. Leukemia. 2013 Apr;27(5):997-9. doi: 10.1038/leu.2012.303. PMID: 23653072.

12. Palmieri R, Othus M, Halpern AB, Percival MM, Godwin CD, Becker PS, Walter RB. Accuracy of SIE/SIES/GITMO Consensus Criteria for Unfitness to Predict Early Mortality After Intensive Chemotherapy in Adults With AML or Other High-Grade Myeloid Neoplasm. J Clin Oncol. 2020 Dec 10;38(35):4163-4174. doi: 10.1200/JCO.20.01392. Epub 2020 Oct 8. PMID: 33030979; PMCID: PMC8462659.

13. Walter RB, Estey EH. Management of older or unfit patients with acute myeloid leukemia. Leukemia. 2015 Apr;29(4):770-5. doi: 10.1038/leu.2014.216. Epub 2014 Jul 9. PMID: 25005246; PMCID: PMC4289127.

14. Stone A, Zukerman T, Flaishon L, Yakar RB, Rowe JM. Efficacy outcomes in the treatment of older or medically unfit patients with acute myeloid leukaemia: A systematic review and meta-analysis. Leuk Res. 2019 Jul;82:36-42. doi: 10.1016/j.leukres.2019.05.007. Epub 2019 May 21. PMID: 31152922.

15. Bell JA, Galaznik A, Huelin R, Stokes M, Guo Y, Fram RJ, Faller DV. Effectiveness and Safety of Therapeutic Regimens for Elderly Patients With Acute Myeloid Leukemia: A Systematic Literature Review. Clin Lymphoma Myeloma Leuk. 2018 Jul;18(7):e303-e314.

doi: 10.1016/j.clml.2018.05.003. Epub 2018 May 10. PMID: 29802009.

16. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017 Jan 26;129(4):424-447. doi: 10.1182/blood-2016-08-733196. Epub 2016 Nov 28. PMID: 27895058; PMCID: PMC5291965.

17. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629. doi: 10.1056/NEJMoa2012971. PMID: 32786187.

18. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. doi: 10.1182/blood.2022016867. PMID: 35797463.

19. Miyamoto, T., Sanford, D., Tomuleasa, C., Hsiao, H.H., Olivera, L.J.E., Enjeti, A.K., et al. (2022). Real-world treatment patterns and clinical outcomes in patients with AML unfit for first-line intensive chemotherapy. Leuk. Lymphoma. 63, 928-938. doi: 10.1080/10428194.2021.2002321.

20. Ito T, Sanford D, Tomuleasa C, Hsiao HH, Olivera LJE, Enjeti AK, et al. Healthcare resource utilization trends in patients with acute myeloid leukemia ineligible for intensive chemotherapy receiving first-line systemic treatment or best supportive care: A multicenter international study. Eur J Haematol. 2022 Jul;109(1):58-68. doi: 10.1111/ejh.13769. Epub 2022 Apr 13. PMID: 35298049; PMCID: PMC9324937.

21. DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018 Feb;19(2):216-228. doi: 10.1016/S1470-2045(18)30010-X. Epub 2018 Jan 12. PMID: 29339097.

22. Bocchia M, Candoni A, Borlenghi E, Defina M, Filì C, Cattaneo C, et al. Real-world experience with decitabine as a first-line treatment in 306 elderly acute myeloid leukaemia patients unfit for intensive chemotherapy. Hematol Oncol. 2019 Oct;37(4):447-455. doi: 10.1002/hon.2663. Epub 2019 Aug 20. PMID: 31385337.

23. Ha H, Jeong Y, Lim JH, Suh YJ. Treatment Pattern, Financial Burden, and Outcomes in Elderly Patients with Acute Myeloid Leukemia in Korea: A Nationwide Cohort Study. Int J Environ Res Public Health. 2022 Feb 17;19(4):2317. doi: 10.3390/ijerph19042317. PMID: 35206499; PMCID: PMC8872510.

24. Yoshida C, Kondo T, Ito T, Kizaki M, Yamamoto K, Miyamoto T, Morita Y, et al. Real-world treatment patterns and clinical outcomes in patients with AML in Japan who were ineligible for first-line intensive chemotherapy. Int J Hematol. 2022 Jul;116(1):89-101. doi: 10.1007/s12185-022-03334-8. Epub 2022 Apr 8. PMID: 35394258.

25. Talati C, Dhulipala VC, Extermann MT, Ali NA, Kim J, Komrokji R, et al. Comparisons of commonly used front-line regimens on survival outcomes in patients aged 70 years and older with acute myeloid leukemia. Haematologica. 2020 Jan 31;105(2):398-406. doi: 10.3324/haematol.2018.208637. PMID: 31073071; PMCID: PMC7012500.

26. Sanford D, Desjardins P, Leber B, Paulson K, Assouline S, Lembo PMC, et al. Real-World Treatment Patterns and Clinical Outcomes in Canadian Patients with AML Unfit for First-Line Intensive Chemotherapy. Curr Oncol. 2022 Sep 22;29(10):6794-6806. doi: 10.3390/curroncol29100535. PMID: 36290812; PMCID: PMC9600019.

27. Sekeres MA, Guyatt G, Abel G, Alibhai S, Altman JK, Buckstein R, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv. 2020 Aug11;4(15):3528-3549.doi: 10.1182/bloodadvances.2020001920. PMID: 32761235; PMCID: PMC7422124.

28. Kennedy VE, Keegan THM, Li Q, Maguire FB, Muffly LS. Frontline treatment patterns and outcomes among older adults with acute myeloid leukemia: A population-based analysis in the modern era. Cancer.

2022 Jan 1;128(1):139-149. doi: 10.1002/cncr.33873. Epub 2021 Aug 26. PMID: 34436782.

29. Turk S, Turk C, Akbar MW, Kucukkaraduman B, Isbilen M, Demirkol Canli S, et al. Renin angiotensin system genes are biomarkers for personalized treatment of acute myeloid leukemia with Doxorubicin as well as etoposide. PLoS One. 2020 Nov 25;15(11):e0242497. doi: 10.1371/journal.pone.0242497. PMID: 33237942; PMCID: PMC7688131.

30. Lyons RM, Potluri J, Bui C, Choi ME, Ma E, Svensson A et al: Treatment outcomes and healthcare resource utilization (HRU) among patients with acute myeloid leukemia (AML) ineligible for intensive chemotherapy in US community oncology setting. Abstr. in: J Clin Oncol 38:e19513-e19513, 2020 (suppl; abstr e19513).

31. Vladescu C, Scintee SG, Olsavszky V, Hernandez-Quevedo C, Sagan A. Romania: Health System Review. Health Syst Transit. 2016 Aug;18(4):1-170. PMID: 27603897.

32. Röllig C, Bornhäuser M, Thiede C, Taube F, Kramer M, Mohr B, et al. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. J Clin Oncol. 2011 Jul 10;29(20):2758-65. doi: 10.1200/JCO.2010.32.8500. Epub 2011 May 31. PMID: 21632498.

33. Antohe I, Dascalescu A, Danaila C,Titieanu A, Dolachi E, Dumitru R et al: The relevance of European leukemia NET recommendations in acute myeloid leukemia. A one center three-year experience. Med Surg J – Rev Med Chir Soc Med Nat, Iaşi 2020;124(2):190-199.

34. Enache AO, Matei M, Lipan LE, Craciun OG, Stefan LD, Stoica AG, Varady Z, Tanase AD. Outcomes of allogeneic stem cell transplantation in acute leukemias single centre study. Documenta Haematologica. 2023;1(4):199-206. DOI: 10.59854/dhrrh.2023.1.4.199.