

Title: Real-world treatment patterns and clinical outcomes in Canadian patients with AML unfit for first-line intensive chemotherapy

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Abstract:

Acute myeloid leukemia (AML) is a hematological malignancy that predominantly affects the elderly. Prognosis declines with age. For those who cannot tolerate intensive chemotherapy, historically established treatment options have been hypomethylating agents (HMAs), low dose cytarabine (LDAC), and best supportive care (BSC). As the standard of care evolves for those unfit for intensive chemotherapy, there is a need to understand established treatment pathways, clinical outcomes and healthcare resource utilization in Canada. The CURRENT study was a retrospective chart review of AML patients not eligible for intensive chemotherapy who initiated first-line treatment between 1 January 2015 and 31 December 2018. Data were collected from 170 Canadian patients treated at six hematology centers, of whom 118 received systemic therapy and 52 received BSC as first-line treatment. Median overall survival was 8.58 months and varied from 2.96 months for BSC to 13.31 months for HMAs. Over 80% of patients had at least one outpatient visit, and 67% of patients receiving systemic therapy and 71% of those receiving BSC had at least one admission to hospital, during their first line of therapy. A total of 96 (81.4%) patients receiving first line systemic therapy and 39 (75.0%) of those receiving first line BSC had at least one red blood cell or platelet transfusion. These findings highlight the unmet need for novel therapies for patients ineligible for intensive chemotherapy.

Keywords: Acute Myeloid Leukemia; Real-world evidence; treatment patterns; chemotherapy-ineligible; outcomes

Introduction:

Acute myeloid leukemia (AML) is a hematologic malignancy characterized by rapid proliferation of undifferentiated myeloid cells in the blood, bone marrow and other tissues.(1) The median age at AML diagnosis is 68 years.(2) Induction chemotherapy followed by post-remission (consolidation) therapy or allogeneic stem cell transplant (SCT) is the standard of care for those who can tolerate such intensive treatment.(3, 4) Overall 5-year survival rates have been reported to range from 19%–29%, but decline with age.(2, 5, 6) Historically, median overall survival (OS) in older AML patients has been poor and a previous registry based study reported OS of 184 days for patients aged 66 – 75 and 80 days for those aged over 76 years.(7) This is in part due to of the age-related increase in frequency of AML with adverse-risk genetics and secondary AML, and/or multidrug resistance, and an inability to physically tolerate intensive chemotherapy due to comorbidities or frailty.(3, 8, 9)

Historically, for patients who are ineligible for intensive chemotherapy the median estimated survival is less than one year. (3, 4, 10) Standard treatment options for these patients have been the hypomethylating agents (HMA) 5-azacitidine (azacitidine)/decitabine, or low-dose cytarabine (LDAC) and best supportive care (BSC) with hydroxyurea or transfusion support.(1) Recently, several novel therapies have been introduced as alternatives for AML patients ineligible for intensive chemotherapy. These include venetoclax, a BCL-2 inhibitor, and glasdegib, a hedgehog pathway inhibitor, both approved by the European Medicines Agency, US Food and Drug Administration and Health Canada (amongst others). Venetoclax is for use with a hypomethylating agent or with LDAC for treatment-naïve elderly AML patients who are ineligible for intensive chemotherapy; glasdegib is approved in combination with low-dose cytarabine, for the treatment

of newly-diagnosed AML in patients ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.(11-16)

As the standard of care (SOC) evolves with novel therapies and rising costs of treatment, there is a need to understand current AML treatment pathways, clinical outcomes including survival, clinicopathologic characteristics, and healthcare resource utilization (HRU) of patients unfit to receive intensive chemotherapy in clinical practice.

Materials and methods:

The Real World Treatment Patterns and Clinical Outcomes in Unfit AML Patients Receiving First Line Systemic Treatment or Best Supportive Care (CURRENT) study was a multicenter, multinational non-interventional retrospective chart review designed to understand the clinicopathologic characteristics, treatment patterns, clinical outcomes (including survival), and HRU of AML patients who are unfit to receive intensive chemotherapy in real world clinical practice.

The study was conducted in accordance with the principles of Good Pharmacoepidemiology Practices and the ethical principles that have their origin in the Declaration of Helsinki. Institutional Review Board/Ethics Committee (IRB/EC). Approval was obtained prior to the initiation of the study as necessary per local regulations (Approval number: H19-02494). Overall results of the study have been published elsewhere,(17) with the results for the Canadian cohort being the focus of this manuscript.

Anonymized medical records of Canadian adults diagnosed with primary or secondary AML between January 01, 2015 and December 31, 2018 were eligible for data extraction if they were

deemed ineligible for intensive chemotherapy and received first-line systemic therapy (including low intensity chemotherapy), targeted therapy or BSC. Those who received first-line therapy as part of a clinical trial were excluded. Data were entered into an online system and a secure database for analysis, storage and reporting.

The primary endpoint for the study was overall survival (OS). Secondary endpoints were progression free survival (PFS), time to treatment failure (TTF), healthcare resource utilization (HRU), measurable residual disease (MRD) testing rates including methodology as available, and rates of complete remission (CR), time to achieve CR, duration of CR, CR with incomplete hematologic recovery (CRi), morphologic leukemia free state (MLFS), partial remission (PR), and treatment failure.

The CURRENT study aimed to capture data from approximately 1600 patients being treated at 175 sites in 30 countries. As the study was descriptive in nature, no formal hypothesis testing or power calculations were required. Data were summarized using descriptive statistics and the Kaplan-Meier method was used to estimate proportions and median times for time-to-event analyses (OS, PFS, TTF). Kaplan Meier curves were presented with two-sided 95% confidence intervals. Differences between subgroups (treatment, risk factors, geography) were explored with log-rank tests and Cox regressions. To mitigate possible sampling bias during site and patient recruitment, specialist sites across Canada were approached to participate in the study. For sites that identified more eligible patients than their enrolment target, instructions for a random sampling method was provided.

Results:

Study population

Overall, data were collected for 1,762 patients with AML from 22 countries. In Canada, data were collected from 170 patients treated at six hematology centers, of whom 118 received systemic therapy and 52 received BSC as first-line treatment. Demographics and baseline characteristics were similar for the two treatment groups (Table 1). Ethnicity was not included as it is not typically captured in patient records in Canada. Overall, 41.8% were aged >75 years, 42.9% had secondary AML, 63.5% had intermediate or poor risk cytogenetics. Of the 96 patients with molecular data, 40 had ≥ 1 mutation, the most common of which were NPM1 (13 patients) and JAK2 (7 patients). Of those with ECOG performance status available, the proportion with ECOG ≥ 2 was higher for those receiving BSC (62.2%) vs those receiving systemic therapy (42.6%), although there were more patients in the systemic therapy group with missing data (60.2% vs 28.8% for BSC). Approximately 10% were hospitalized for leukemia treatment initiation.

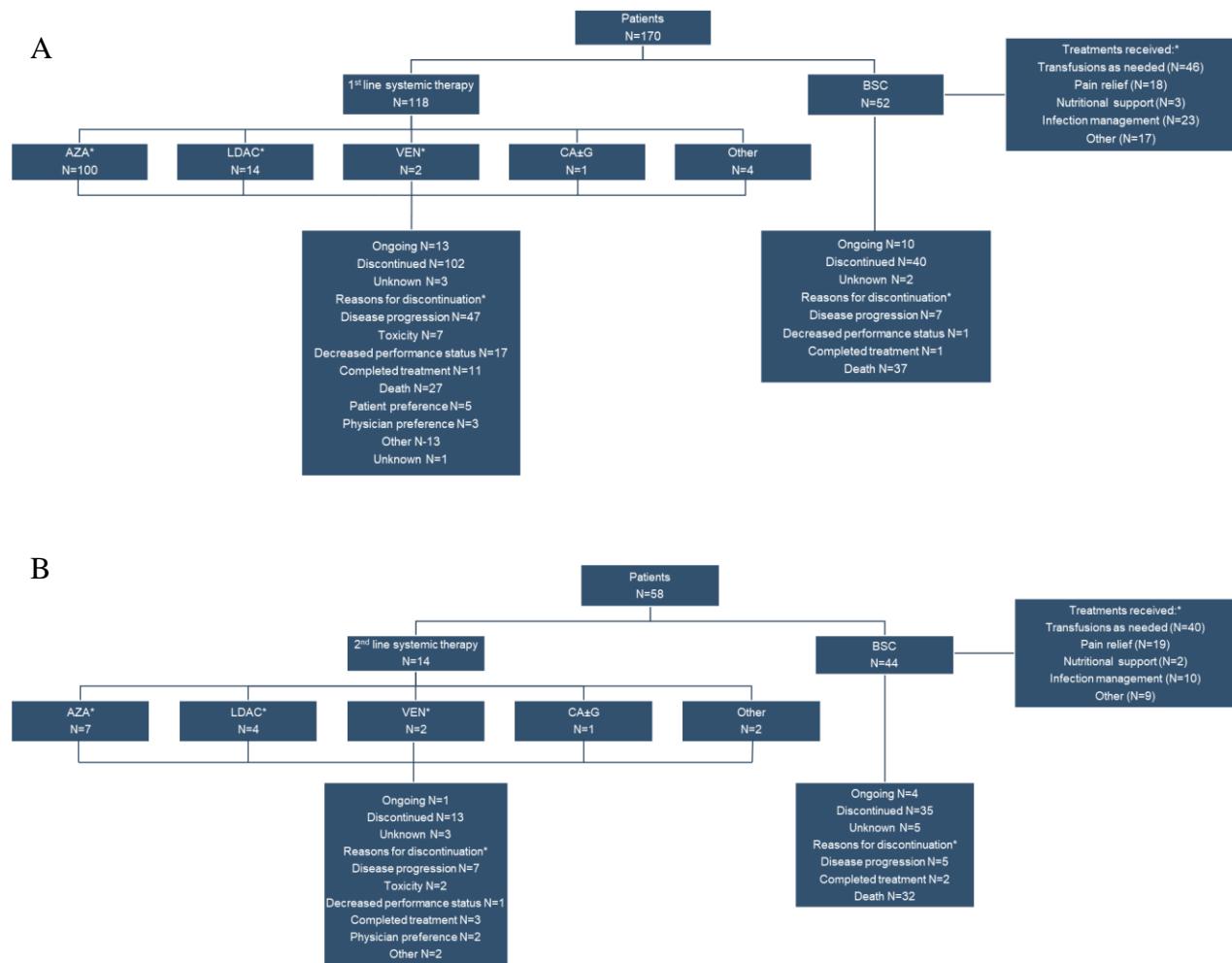
Treatment patterns

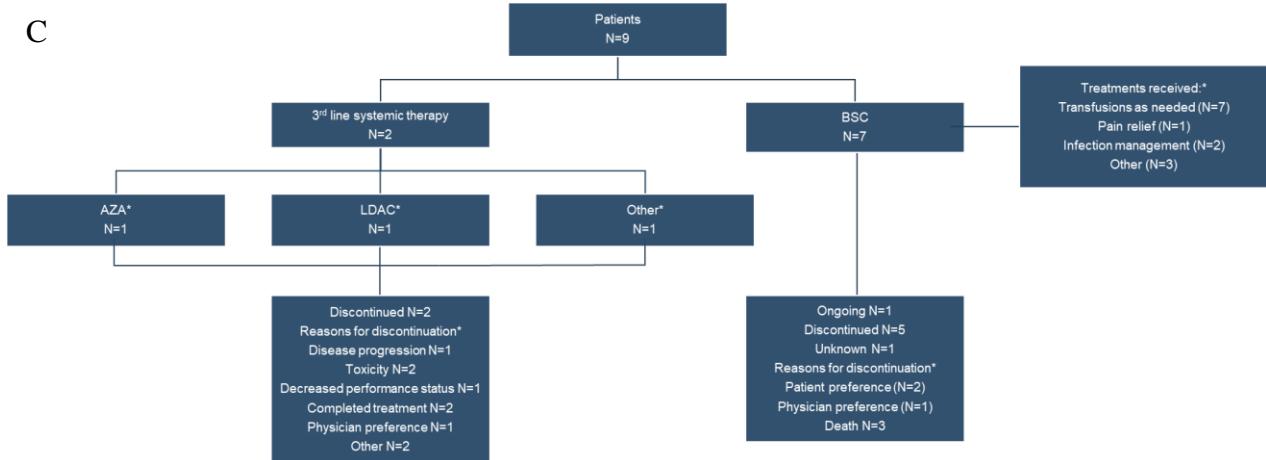
The 118 patients who received systemic therapy as first line treatment received a median (range) of 5 (1 – 62) cycles, typically with AZA (n=100, 84.7%) or LDAC (n=14, 11.9%). Fourteen patients received systemic therapy as second line treatment, but for a median (range) of 3.5 (1 – 27) cycles. Only two patients received a third line of systemic therapy (Figure 1). Among those who received BSC, the most common interventions were transfusions, other, infection management and pain relief (Figure 1). The most common reasons for discontinuation of systemic therapy were disease progression (n=47, 46.1%), death (n=27, 26.5%), decline in performance status (n=17, 16.7%) and other (n=13, 12.7%) for first line therapy. For 2nd line systemic therapy the most common reasons for discontinuation were disease progression (n=7, 53.8%) and completed planned treatment (n=3, 23.1%). For those receiving BSC, the most

common reason for treatment discontinuation was death (n=37, 92.5% for 1st line, n=32, 91.4% for 2nd line treatment).

Figure 1. First-line (A), second-line (B) and third-line (C) treatment patterns and disposition of Canadian patients ineligible for high intensity chemotherapy.

*Patients may be taking more than one systemic therapy simultaneously. AZA, 5-azacytidine; BSC, best supportive care; CA±G, cytarabine, aclarubicin, G-CSF regimen; G-CSF, Granulocyte - colony stimulating factor; LDAC, low-dose cytarabine; VEN, venetoclax.

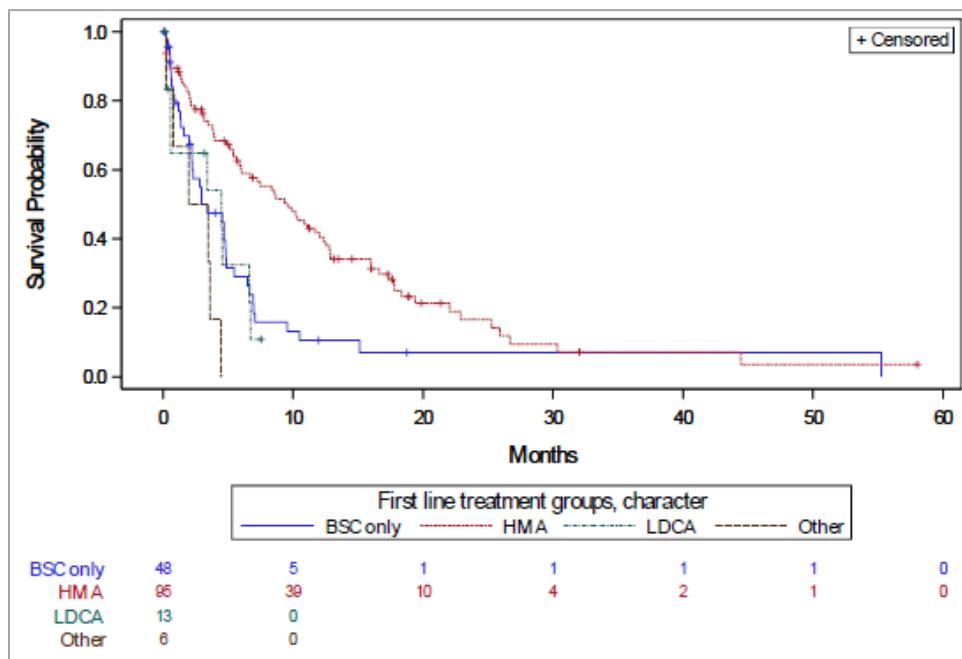




Overall survival

The median survival for the overall population was 8.58 months (95% confidence interval [CI]: 6.2 – 11.1 months) and varied by first-line treatment from 2.96 (2.2 – 4.9) months for BSC to 13.31 (10.0 – 15.2) months for HMAs (Figure 2, Table 2). Overall survival was 20.5% (95% CI: 13.8 – 28.4%) at two years and 3.2% (95 CI: 0.3 – 12.7%) at five years.

Figure 2. Time to treatment failure by first-line treatment received.



Overall, the most common cause of death was AML progression (68.9%), infection (17.2%) and unknown (8.2%), with similar rates for first-line systemic therapy and BSC (Table 3).

Similar survival patterns were observed for PFS and TTF (Table 2), with an apparent increase in median time to PFS and TTF for patients receiving first line HMAs, compared with those who received BSC, and LDAC intermediate.

Treatment response

Best treatment response was unknown for approximately half of patients (Table 4). Few patients achieved a best overall response of CR or CRi with first- or second-line systemic therapy. It is interesting to note that two patients received venetoclax combination therapy as first line, and another two received it as second line, systemic therapy.

Healthcare resource utilization

During their first line of therapy, over 80% of patients had at least one outpatient visit with a median of 10 visits for patients receiving systemic therapy and 6 for those receiving BSC (Table 5). In addition, 79 (66.9%) patients receiving systemic therapy and 37 (71.2%) of those receiving BSC had at least one admission to hospital (the median number of hospitalizations per patient was 1 for both groups). The median duration of stay was 7 days for those receiving systemic therapy and 9 days for those receiving BSC. The most common reason for hospitalization for both groups during the first line of therapy was infection-related (52.2% of admissions for patients receiving systemic therapy; 60.9% of those receiving BSC). A total of 96 (81.4%) patients receiving first line systemic therapy and 39 (75.0%) of those receiving first line BSC had at least one RBC or platelet transfusion (median: 10 RBC transfusions for patients receiving systemic therapy and 6 for those receiving BSC. The median number of platelet transfusions was 1.5 for both groups).

Only 3 patients receiving their first line of systemic treatment had an assessment for MRD. All three assessments were performed on bone marrow aspirate samples.

Antibiotics or antivirals were used by approximately half of patients during their first line of therapy, almost always for curative purposes (Table 6). Use of antifungal therapy was much less common and occurred at least once in 21 (17.8%) and 3 (5.8%) of patients receiving first line systemic therapy and BSC, respectively.

Discussion:

This analysis of the CURRENT non-interventional retrospective chart review dataset highlights the real-world characteristics, treatment patterns, clinical outcomes and HRU of Canadians with AML who are unfit to receive intensive chemotherapy. As patients eligible for intensive chemotherapy were excluded from the study, this cohort provides an overview of the demographics and characteristics of patients on other therapeutic options. To mitigate possible sampling bias, specialist sites across Canada were approached to participate in the study and sites that identified more eligible patients than their enrolment target were provided with a random sampling method.

Approximately 40% were female, consistent with other Canadian data,(18) and 60% were at least 75 years old at diagnosis. As would be expected for an older cohort, a high proportion (39%) had a poor cytogenetic risk profile,(8) and just under 80% had at least one co-morbidity. Baseline characteristics for those patients who received first line systemic therapy were generally similar to those who elected BSC. The exception to this was performance status (which was worse for patients who received BSC), although it should be noted that performance status was

unknown for 60% of patients who received systemic therapy compared with 29% of those who received BSC.

Consistent with treatment recommendations when the medical records were generated, treatment options in this intensive chemotherapy-ineligible population were generally AZA, LDAC and BSC.(3, 4) Thirty percent of the Canadian cohort was treated with BSC as first line therapy which is consistent with the results from the CURRENT study as a whole (26% received BSC).(17) The proportion of patients who received an HMA as first line systemic therapy was greater in the Canadian than the overall cohort (85% vs 66%, respectively) while the respective proportions receiving LDAC were similar (12% vs 15%, respectively). The disparity in first line systemic treatment choices appear to be related predominately to higher use of cytarabine, aclarubicin, granulocyte colony stimulating factor combination (CAG) elsewhere (0.8% vs 19%, respectively). Use of novel targeted agents was low in both cohorts, presumably reflecting the exclusion of patients who received treatment as part of a clinical trial and the limited availability of novel agents such as venetoclax or glasdegib for older patient during the study period. The proportion of Canadian patients who received a second line of systemic therapy was lower than that observed in the overall CURRENT cohort (12% vs 18%, respectively). Among potential explanations for this is differences in reimbursement policies between participating countries (and also between Canadian Provincial drug plans)

Median survival was numerically longer in the Canadian cohort than in the overall CURRENT population (8.58 months vs 6.2 months, respectively), which may reflect differences in demographics, baseline characteristics, use of systemic therapies and supportive care. What was consistent was the abysmal life expectancy of patients selecting first line BSC, with a median OS of less than three months in both cohorts. Also consistent was the association between systemic

therapy type and survival, with HMAs providing the longest OS (13.3 months for the Canadian cohort vs 9.9 months for the overall population) and LDAC being intermediate (6.4 months for the Canadian cohort vs 7.9 months for the overall population). Overall, however, life expectancy and clinical outcomes in this population remain extremely poor.

This analysis of healthcare resource utilization provided important data for non-intensively treated AML patients in Canada, and there are few other published multicenter Canadian studies in this area. The number of patients requiring at least one hospitalization during the first line of therapy was similar for first line systemic therapy and BSC and although the proportion of patients requiring ≥ 3 hospitalizations was numerically higher for the systemic therapy group, the median duration was longer, and there was a greater requirement for intensive care beds for those receiving BSC. This data suggests that use of a BSC strategy does not significantly reduce hospitalizations. As expected, there were more outpatient visits for patients receiving systemic therapy. This group required more transfusions, but may reflect longer survival compared with patients who selected BSC. These data suggest real-world healthcare resource utilization may be only marginally impacted by treatment choice, unlike clinical outcomes.

The CURRENT study is one of the largest, global, real-world studies performed to date of treatment patterns in patients with AML who were ineligible for intensive chemotherapy. The Canadian dataset provides valuable insights into the real-world characteristics, treatment patterns, clinical outcomes and HRU of Canadians with AML who are unfit to receive intensive chemotherapy. Several limiting factors should be considered when interpreting these results. Real-world, retrospective studies are by nature observational, uncontrolled and nonrandomized, and missing data limit the implications of some endpoints. Molecular and cytogenetic data, and performance status, were often not recorded, which limited assessment of their impact on

outcomes, and some endpoints (e.g., type of BSC provided, best overall response achieved) elicited a high number of responses as “other” or “unknown” which challenged interpretation. While the six Canadian sites provide strong regional representation, there was no site from Atlantic Canada. All the sites involved in the study were academic centers and as such may not necessarily represent treatment patterns or outcomes for patients treated in rural areas and smaller centers. Within participating sites there was also the potential for selection bias when considering patients’ medical records for data extraction. Sample size considerations obviated the potential for exploration of regional differences. Finally, the data capture period for the study preceded approval of newer targeted therapies in many jurisdictions and thereby provided an assessment of treatments that may now be considered foundational.

Conclusions

Overall, this analysis confirms that historical outcomes in patients with AML who were ineligible for intensive chemotherapy were poor, with HMAs demonstrating a benefit over alternatives. As the incidence of AML rises consequent to an aging population, so does the number of patients who are ineligible for intensive chemotherapy, highlighting the clinical need for novel agents and combination therapies that are both effective and appropriate for use in this treatment-challenged population. Since the collection of these data, the use of novel targeted therapies in Canada has increased, improving the outcome of such patients.

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Table 1. Patient demographics and baseline characteristics.

	Overall (n=170)	1 st line systemic therapy (n=118)	BSC (n=52)
Female gender (n [%])	65 (38.2)	41 (34.7)	24 (46.2)
Mean (SD) age at diagnosis (years)	74.3 (7.01)	74.3 (6.90)	74.3 (7.37)
≤75 years (n [%])	99 (58.2)	71 (60.2)	28 (53.8)
Secondary AML			
Yes	73 (42.9)	44 (37.3)	29 (55.8)
No	79 (46.5)	59 (50.0)	20 (38.5)
Unknown	18 (10.6)	15 (12.7)	3 (5.8)
ECOG performance status			
0-1	41 (24.1)	27 (22.9)	14 (26.9)
≥2	43 (23.5)	20 (17.0)	23 (44.2)
Unknown	86 (50.6)	71 (60.2)	15 (28.8)
AML classification – WHO (n [%])			
AML with recurrent abnormalities	13 (7.6)	11 (9.3)	2 (3.8)
AML with MDS-related changes	76 (44.7)	53 (44.9)	23 (44.2)
AML not otherwise specified	41 (24.1)	28 (23.7)	13 (25.0)
Myeloid sarcoma	1 (1.2)	0	2 (3.8)
Unknown	33 (19.4)	22 (18.6)	11 (21.2)
Cytogenetic risk (n [%])			
Favourable	26 (15.3)	19 (16.1)	7 (13.5)
Intermediate	47 (27.6)	38 (32.2)	9 (17.3)
Poor	61 (35.9)	46 (39.0)	15 (28.8)
Unknown	36 (21.2)	15 (12.7)	21 (40.4)
Molecular features identified (n [%])			
Any	40 (23.5)	30 (25.4)	10 (19.2)

IDH2	1 (2.5)	1 (3.3)	0
TP53	2 (5.0)	2 (6.7)	0
TET2	1 (2.5)	1 (3.3)	0
RUNX1	5 (12.5)	3 (10.0)	2 (20.0)
DNMT3A	1 (2.5)	1 (3.3)	0
ASXL 1	3 (7.5)	3 (10.0)	0
FLT3 ^{TKD}	2 (5.0)	2 (6.7)	0
JAK2	7 (17.5)	3 (10.0)	4 (40.0)
NPM1	13 (32.5)	10 (33.3)	3 (30.0)
SRSF2	2 (5.0)	2 (6.7)	0
MLLPTD	2 (5.0)	1 (3.3)	1 (10.0)
Other	11 (27.5)	9 (30.0)	2 (20.0)
None	56 (32.9)	42 (35.6)	14 (26.9)
Unknown	74 (43.5)	46 (39.0)	28 (53.8)
Co-morbidities (n [%])			
Myocardial infarction	2 (1.2)	1 (0.8)	1 (1.9)
Angina/coronary artery disease	22 (12.9)	12 (10.2)	10 (19.2)
Congestive heart failure	11 (6.5)	8 (6.8)	3 (5.8)
Arrhythmias	14 (8.2)	9 (7.6)	5 (9.6)
Restrictive lung disease or COPD	8 (4.7)	8 (6.8)	0
Liver cirrhosis (Child Pugh A, B or C)	1 (0.6)	1 (0.8)	0
Elevated transaminases unrelated to cirrhosis	1 (0.6)	1 (0.8)	0
CKD stage 3, 4 or 5	2 (1.2)	0	2 (3.8)
Other	99 (58.2)	69 (58.5)	30 (57.7)
Unknown	15 (8.8)	9 (7.6)	6 (11.5)
None	39 (22.9)	27 (22.9)	12 (23.1)

AML, acute myeloid leukemia; ASXL 1, ASXL transcriptional regulator 1; BSC, best supportive care; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DNMT3A, DNA methyltransferase 3 alpha;

FLT3^{TKD}, FLT3 tyrosine kinase domain; IDH2, isocitrate dehydrogenase 2; JAK2, Janus kinase 2; MDS, myelodysplastic syndrome; MLLPTD, mixed-lineage leukemia gene-partial tandem duplication; NPM1, nucleophosmin 1; RUNX1, runt-related transcription factor 1; SRSF2, serine and arginine rich splicing factor 2; TET2, tet methylcytosine dioxygenase 2; TP53, tumor protein P53; WHO, whorl health organization

Table 2. Kaplan-Meier estimates of survival

	Overall (n=170)	LDAC (n=14)	HMA (n=97)	Other (n=7)	BSC only (n=52)
Median (95% CI) OS (months)	8.6 (6.2 – 11.1)	6.4 (5.0 – 14.2)	13.1 (10.0 – 15.2)	NE	3.0 (2.2 – 4.9)
Median (95% CI) PFS (months)	5.8 (4.4 – 7.2)	5.5 (1.4 – 12.9)	9.7 (7.2 – 11.4)	3.6 (1.5 – NE)	2.4 (1.2 – 3.2)
2-year (95% CI) OS (%)	20.5 (13.8 – 28.2)	11.7 (0.7 – 39.4)	26.9 (17.2 – 37.4)	62.5 (14.2 – 89.3)	6.7 (1.4 – 17.9)
5-year (95% CI) OS (%)[*]	3.2 (0.3 – 12.7)	0	4.7 (0.5 – 17.4)	0	0

* Last observation was censored before Month 60; results for Month 59 are presented here. BSC, best supportive care; HMA, hypomethylating agents; LDAC, low-dose cytarabine; OS, overall survival; PFS, progression-free survival.

Table 3. Patient outcomes at end of study

	Overall (n=170)	1 st line systemic therapy (n=118)	BSC only (n=52)
Alive at end of study	48 (28.2)	37 (31.4)	11 (21.2)
Cause of death (n [%]):			
AML progression	84 (68.9)	56 (69.1)	28 (68.3)
Infection	21 (17.2)	16 (19.8)	5 (12.2)
Multi-organ failure	1 (0.8)	16 (19.8)	1 (2.4)
Other comorbid conditions	5 (0.1)	3 (3.7)	2 (4.9)
Unrelated to a disease	1 (0.8)	3 (3.7)	1 (2.4)
Unknown	10 (8.2)	6 (7.4)	4 (9.8)

AML, acute myeloid leukemia; BSC, best supportive care.

Table 4. Best overall response to first- and second-line therapy.

Best overall response (n, %)	First line therapy (n=118)	Second line therapy (n=14)
CR	10 (8.5)	1 (7.1)
CRi	8 (6.8)	0
PR	18 (15.3)	4 (28.6)
SD	21 (17.8)	0
PD	12 (10.2)	2 (14.3)
Unknown	49 (41.5)	7 (50.0)

CR, complete remission; CRi, CR with incomplete hematologic recovery; PD, progressive disease; PR, partial remission; SD, stable disease.

Table 5. Healthcare resource utilization during first-line therapy

	Systemic therapy (n=118)	BSC (n=52)
Outpatient consultation (N [%]):		
Yes*	96 (81.4)	43 (82.7)
No	18 (15.3)	5 (9.6)
Unknown	4 (3.4)	4 (7.7)
Number of visits (median [range])	10 (1 – 105)	6 (1 – 80)
Hospitalization (N [%]):		
Yes*	79 (66.9)	37 (71.2)
No	36 (30.5)	8 (15.4)
Unknown	3 (2.5)	7 (13.5)
Number of hospitalizations (N [%]):		
1	50 (63.3)	27 (73.0)
2	19 (24.1)	7 (18.9)
≥3	10 (12.7)	3 (8.1)
Duration of stay (days, median [range])		
Overall	7 (1 – 100)	9 (1 – 92)
In ICU	0 (0 – 31)	2 (0 – 38)
Reason for hospitalization: [†]		
Progression/relapse-related	22 (16.4)	19 (34.5)
Infection-related	70 (52.2)	32 (58.2)
Transfusion-related	9 (6.7)	4 (7.3)
Treatment administration-related	14 (10.4)	3 (5.5)
Other AML-related	25 (18.7)	10 (18.2)
Other	38 (28.4)	10 (18.2)
RBC/PLT transfusion (N [%]):		
Yes	96 (81.4)	39 (75.0)

No	16 (13.6)	7 (13.5)
Unknown	6 (5.1)	6 (11.5)
If yes, number of RBC transfusions (median [range])	10 (2 – 180)	6 (1 – 100)
If yes, number of PLT transfusions (median [range])	1.5 (0 – 50)	1.5 (0 – 200)

*Where applicable, this value is used as the denominator for calculating percentages, and only those patients with at least one outpatient consultation/hospitalization were included in calculations of medians and ranges for number of visits and length of stay, respectively. †Multiple selections were possible.

AML, acute myeloid leukemia; BSC, best supportive care; ICU, intensive care unit; PLT, platelet; RBC, red blood corpuscle.

Table 6. Anti-infective use

	Systemic therapy	BSC
First line therapy	n=118	n=52
Antibiotic or antiviral use (N [%]):		
Yes*	63 (53.4)	29 (55.8)
No	54 (45.8)	16 (30.8)
Unknown	1 (0.8)	7 (13.5)
Reason for use: [†]		
Prophylaxis	16 (25.4)	3 (10.3)
Curative	51 (81.0)	27 (93.1)
Unknown	3 (4.8)	0
Antifungal use (N [%]):		
Yes*	21 (17.8)	3 (5.8)
No	96 (81.4)	44 (84.6)
Unknown	1 (0.8)	5 (9.6)
Reason for use: [†]		
Prophylaxis	11 (52.5)	1 (33.3)
Curative	8 (38.1)	2 (66.7)
Unknown	2 (9.5)	0
Second line therapy	n=14	n=44
Antibiotic or antiviral use (N [%]):		
Yes*	6 (42.9)	17 (38.6)
No	7 (50.0)	21 (47.7)
Unknown	1 (7.1)	6 (13.6)
Reason for use: [†]		
Prophylaxis	1 (16.7)	6 (35.3)
Curative	6 (100.0)	10 (58.8)

Unknown	0	2 (11.8)
Antifungal use (N [%]):		
Yes*	2 (14.3)	8 (18.2)
No	12 (85.7)	30 (68.2)
Unknown	0	6 (13.6)
Reason for use: [†]		
Prophylaxis	1 (50.0)	4 (40.0)
Curative	1 (50.0)	3 (37.5)
Unknown	0	1 (12.5)
Third line therapy	n=2	n=7
Antibiotic or antiviral use (N [%]):		
Yes*	2 (100.0)	3 (42.9)
No	0	4 (57.1)
Reason for use: [†]		
Prophylaxis	1 (50.0)	0
Curative	1 (50.0)	3 (100.0)
Unknown	1 (50.0)	0
Antifungal use (N [%]):		
Yes*	2 (100.0)	2 (28.6)
No		5 (71.4)
Reason for use: [†]		
Prophylaxis	1 (50.0)	0
Curative	1 (50.0)	2 (100.0)
Unknown	1 (50.0)	0

*Value used as the denominator for calculating percentages. [†]Multiple selections were possible.

BSC, best supportive care.

Figure legends

Figure 1. First-line (A), second-line (B) and third-line (C) treatment patterns and disposition of Canadian patients ineligible for high intensity chemotherapy.

*Patients may be taking more than one systemic therapy simultaneously. AZA, 5-azacytidine; BSC, best supportive care; CA±G, cytarabine, aclarubicin, G-CSF regimen; G-CSF, Granulocyte - colony stimulating factor; LDAC, low-dose cytarabine; VEN, venetoclax.

Figure 2. Time to treatment failure by first-line treatment received.