Patient-centered care strategies for Jehovah's Witnesses with acute leukemia and high-grade myeloid neoplasms

Jehovah's Witnesses (JW) commonly choose not to receive transfusions of whole blood and its components for religious reasons, necessitating alternative strategies in the treatment of acute leukemia and high-grade myeloid neoplasms. Although remission can be achieved through tailored, transfusion-free strategies, survival outcomes, especially for acute myeloid leukemia (AML), remain inferior compared to those of patients receiving transfusion support. The clinical management of JW patients requires nuanced approaches due to significant individual variability in the acceptance of specific treatments. Although JW often forgo transfusions of whole blood and primary blood components, decisions about accepting fractions derived from blood, such as erythropoiesis-stimulating agents (ESA; containing albumin), thrombopoietin receptor agonist (TPO-RA), granulocyte colony-stimulating factor (G-CSF), immunoglobulins, clotting factors, and hemoglobin solutions vary based on individual personal beliefs. Furthermore, acceptance of stem cell transplantation (SCT) among JW patients is heterogeneous.

Several reports illustrate the feasibility and limitations of transfusion-free leukemia care. Cullis *et al*. reported outcomes in three JW patients with acute lymphoblastic leukemia (ALL) and two JW patients with AML.[1] Patients with ALL achieved remission with fairly intensive therapies without transfusion support while outcomes in the patients with AML were less favorable.[1] Similarly, in a case series from Laszlo *et al*., four of five patients with ALL but only one of six with AML achieved complete remission (CR).[2] Other case reports describe similar outcomes across AML[3-6] and ALL.[7] Tailored strategies that may facilitate transfusion-free care include (i) lower-intensity and thus less myelosuppressive therapies,[8,9] such as the doublet of azacitidine and venetoclax in AML,[8] (ii) the use of hematopoietic growth factors,[10] or (iii) the use of blood substitutes.[11] Our experience emphasizes the critical need for individualized care, incorporating targeted leukemia therapies, and prophylactic implementation of supportive hematopoietic agents to improve patient outcomes.

After institutional review board approval, the Mayo Clinic electronic health record was retrospectively reviewed to identify JW patients diagnosed with acute leukemia or myelodysplastic syndrome (MDS) with increased blasts, as classified by the World Health Organization 5th edition criteria.[12] Response was assessed based on standard criteria for AML,[13] ALL,[14] and MDS.[15]

We identified 13 patients meeting inclusion criteria; two patients accepted blood transfusion and were excluded from this report. Our series (median age of 66.5 years, 54.5% female) consisted of four patients with AML, four with MDS with increased blasts (MDS-IB1/IB2), one patient with chronic myelomonocytic leukemia (CMML-2), and two with ALL. Among the AML patients, there was one core-binding factor AML, two myelodysplasia-related changes, and one chronic myeloid leukemia in blast phase (CML-BP). Of the two ALL patients, one had Philadelphia-like B-ALL and one had Philadelphia-positive ALL. At diagnosis, baseline hemoglobin (Hgb) levels ranged from 5.2 g/L to 11.9 g/dL, and platelet counts ranged from $27x10^9$/L to $248x10^9$/L. The median follow-up duration was 5.7 months (range, 1-33 months), and the median overall survival (OS) was 5.7 months. All patients survived at least 4 weeks post-diagnosis.

Five of six patients with acute leukemia received active treatment. Regimens included attenuated decitabine plus venetoclax, azacitidine plus sorafenib, and dasatinib plus HyperCVAD. None of the AML patients in our cohort received intensive chemotherapy. Among the two treated with lower-intensity regimens, AML-2 achieved a meaningful and prolonged response with azacitidine plus sorafenib completing 19 cycles followed by azacitidine plus venetoclax for seven cycles. Importantly, the patient never received transfusion support and was treated with epoetin α and romiplostim during periods of profound anemia and thrombocytopenia, highlighting that disease control can be achieved with HMA-based therapy even in the absence of transfusions. The patient died of a cardiac arrest in the context of a Hgb of 1.8 g/dL while on gilteritinib monotherapy after progression. AML-4 (CML-BP) was treated with targeted therapy (ponatinib, then dasatinib followed by asciminib), which, while not classically myelosuppressive, was effective; the patient was treated with epoetin α for anemia and never required thrombopoietic support. Both patients with ALL received intensive chemotherapy. ALL-5 (Philadelphia-positive ALL) received eight cycles of HyperCVAD plus dasatinib with a Hgb nadir of 9 g/dL, an uncommon outcome for a myelosuppressive regimen. This stability likely reflects the benefit of proactive ESA and romiplostim support. The patient subsequently relapsed, was treated with ponatinib and blinatumomab, underwent an allogeneic peripheral blood SCT at an outside institution using a bloodless protocol, but ultimately died from complications of gastrointestinal graft-*versus*-host disease. These cases highlight that, with carefully tailored regimens and diligent supportive care, meaningful survival can be achieved even in the absence of transfusions. AML-1 died from a myocardial infarction (MI) attributed to severe anemia (Hgb 2.4 g/dL). AML-3 did

Table 1. Clinical characteristics, treatment strategies, and outcomes of Jehovah's Witnesses with acute leukemia and high-grade myeloid neoplasms treated at Mayo Clinic.

Patient#	Age/ sex	Diagnosis per WHO 5th edition	Cytogenetics	Mutations/ fusions	Hgb Nadir, g/dL	Platelet Nadir, x10⁹/L	Supportive treatments				Treatment	OS, months	Outcome	Cause of death
							Erythroid support	Platelet support	G-CSF	IV iron				
AML-1	67/F	AML with *CBFB::MYH11* fusion	46,XX,inv(16)(p13.1q22)[20]	*PPM1D* *CBFB::MYH11* fusion	2.4	12	Epo α 40,000 u BIW at Hgb 7.3 g/dL → QD at Hgb 5.9 g/dL	Romi 2 μg/kg QW at plt 25/μL → increased to 4 μg/kg QW	No	Yes	dec (5 d) + ven (7 d) x 1 cycle	2.4	D	MI from anemia
AML-2	58/F	AML, myelodysplasia-related	46,XX,der(7)t(7;11)(q11.2;q13)[20]	*EZH2* *FLT3-TKD*	1.8	5	Epo α 40,000 u QW at Hgb 5.8 g/dL but Hgb continued to drop to 1.8 g/dL	Romi 1 μg/kg QW at plt 22/μL but continued to drop to 5/μL	No	Yes	7 d of aza + sorafenib x 19 cycles → aza (5 d)/ven (28 d) x 7 cycles → gilt x 1 cycle	32.9	D	Cardiac arrest from anemia
AML-3	74/F	AML, myelodysplasia-related	46, XX[20]	*ASXL1* *CALR*	5.4	201	-	-	No	No	-	7.0	D	Disease progression
AML-4	69/F	CML, *BCR::ABL1*-positive, blast phase	Complex	*BCR::ABL1* *STAG2* *CALR* *MPL*	4.4	103	Darbepo α 2.25 μg/kg Q3W initially → epo α 60,000 u monthly at Hgb of 4.9 g/dL, Hgb increased to 9.9 g/dL	-	No	Yes	Ponatinib → dasatinib → asciminib	10+	L	-
ALL-5*	45/M	B-ALL with *BCR::ABL1* fusion	Complex monosomal	*BCR::ABL1* fusion	9	9	Epo α 40,000 u QW at Hgb 11.7 g/dL → stopped at Hgb 9.3 g/dL	Romiplostim 4 μg/kg QW at plt 159x10⁹/L and stopped at 203x10⁹/L	Yes	No	Dasatinib + HyperCVAD x 8 cycles → POMP + dasatinib x 1 cycle → Blina + ponatinib x 2 cycles → alloSCT (bloodless regimen with Flu TBI)	19	D	Acute GVHD
ALL-6	32/M	B-ALL with *BCR::ABL1*-like features	46, XY[20] (FISH positive for *CRLF2::IGH* fusion)	*CRLF2::IGH* fusion	5.6	46	Epo α 40,000 u QW at Hgb 5.6 g/dL, stopped at Hgb 11.8 g/dL	-	Yes	Yes	Cy + topotecan + dex x 1 cycle → Blina (partial cycle) → Cy + topotecan x 1 cycle → Cisplatin + etoposide	4.3	D	Neuroblastoma progression (ALL in MRD positive CR)
MDS-7	65/F	MDS-IB1	46,XX[7]	*SF3B1*	2.9	40	Epo α 40,000 u QW at Hgb 5.1 g/dL	-	No	Yes	Luspatercept 1 mg/kg Q3W	33	D	Disease progression
MDS-8	59/M	MDS-IB1	Complex monosomal	*TP53*	7.9	27	-	Eltrombopag 75 mg daily at plt 27x10⁹/L	No	No	-	2.0	D	Disease progression
MDS-9	66/M	MDS-IB1	Complex monosomal	*TP53*	5.2	52	-	-	No	No	-	1.8	D	Disease progression
MDS-10	79/M	CMML-2	46,XY,t(10;14)(q11.2;q24)?c[20]	*BCOR* *NRAS* *RUNX1* *SRSF2* *TET2*	4.7	3	-	-	No	No	-	13.1	D	Disease progression
MDS-11	82/F	MDS-IB2	Complex	*SF3B1* *DDX41*	3.6	46	Epo α 60,000 u at Hgb 5.6 g/dL, no response	-	Yes	No	Azacitidine x 3 days	2.3	D	Neutropenic Sepsis

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ALL: acute lymphoblastic leukemia; alloSCT: allogeneic stem cell transplant; AML: acute myeloid leukemia; Aza: azacitidine; BIW: twice weekly; blina: blinatumomab; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; Cy: cyclophosphamide; D: deceased; d: days; dec: decitabine; dex: dexamethasone; darbepo α: darbepoetin α; epo α: epoetin α; F: female; Flu: fludarabine; G-CSF: granulocyte colony-stimulating factor; Hgb: hemoglobin; HyperCVAD: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, Methotrexate, Cytarabine; gilt: gilteritinib; GVHD: graft-*versus*-host disease; IV: intravenous; L: alive; M: male; MDS-IB: myelodysplastic syndrome with increased blasts; MI: myocardial infarction; MRD: measurable residual disease; OS: overall survival; Plt: platelets; POMP: Prednisone, Vincristine, Methotrexate, Mercaptopurine; Q3W: every 3 weeks; QD: daily; QW: weekly; romi: romiplostim; TBI: total body irradiation; u: units; ven: venetoclax; w: weeks; WHO: World Health Organization. → Indicates next treatment. *ALL-5 underwent allogeneic SCT at an outside institution; performed with transfusion-free intent per patient preference. All patients followed microdraw/limited phlebotomy protocols. Additional supportive measures (where applicable): vitamin K (N=2), antifibrinolytics (tranexamic acid or aminocaproic acid; N=3), supplemental oxygen (N=4, all with Hgb <7 g/dL).

not receive leukemia-directed therapy.

Two of five patients with MDS received active treatment. MDS-7 remained untreated for 1 year before initiating luspatercept, which was continued for another year then discontinued due to disease progression. The patient also received epoetin α, though its effect diminished over time. Another patient with MDS (MDS-11) received 3 days of azacitidine and died of complications of neutropenic sepsis. Further details are included in Table 1.

Supportive care was integral to effective leukemia management, and its absence or delay was associated with adverse outcomes. Three (27%) patients (AML-3, MDS-9 and MDS-10) transitioned directly to comfort-focused care without supportive treatment; all others received ESA and/or TPO-RAs (Table 1). For example:

- AML-4 (CML-BP) had a favorable response, with hemoglobin improving from 4.9 g/L to 9.9 g/dL on ESA therapy.
- ALL-5 maintained hemoglobin ≥9 g/dL during eight cycles of HyperCVAD, a rare outcome in a myelosuppressive regimen, suggesting benefit from ESA.
- ALL-6 demonstrated a clear erythroid response from ESA with Hgb rising from 5.6 g/L to 11.8 g/dL, which enabled chemotherapy delivery and provided a 4-month palliative benefit despite a competing neuroblastoma.
- In contrast AML-1, AML-2 showed no erythroid benefit, with progressive anemia contributing to fatal cardiac events, and both MDS-7 and MDS-11 had no improvement despite ESA use.

Four patients received TPO-RA:

- AML-1 showed a good platelet response to romiplostim. However, given that this patient only received a single cycle of decitabine plus venetoclax, it is possible the platelet recovery was due to cessation of myelosuppressive therapy or response to therapy rather than a pharmacologic effect of romiplostim.
- ALL-5 benefited from romiplostim, achieving platelet stabilization that allowed the patient to complete induction, consolidation, and maintenance chemotherapy plus dasatinib. This support also facilitated subsequent salvage therapy upon relapse and a transfusion-free allogeneic SCT at an outside institution.
- AML-2 (MDS-related) received romiplostim without platelet improvement, with counts continuing to decline despite therapy.
- MDS-8 received eltrombopag with no response and ultimately transitioned to hospice.

Five patients received intravenous iron supplementation either once or every 3 weeks; none showed meaningful improvement in Hgb. Two patients (AML-1, ALL-5) received vitamin K for bleeding prophylaxis - AML-1 at 1 mg daily for 1 week and ALL-5 at 10 mg weekly for 3 weeks. Additionally, three patients (AML-1, AML-2, and ALL-6) received antifibrinolytics (tranexamic acid or aminocaproic acid). All patients underwent micro draw (0.5 mL) and/or limited/minimal blood draw (1-1.5 mL) protocols to minimize iatrogenic blood loss. Four patients required supplemental oxygen therapy for hypoxia when Hgb levels were below 7 g/dL. No patients received blood substitutes due to lack of institutional availability (Table 1).

While our experience and the existing literature show that managing acute leukemia and high-grade myeloid neoplasms without transfusion support in JW is feasible, survival outcomes, particularly in AML, remain inferior compared to transfused patients.[6] Importantly, most reported data predate the widespread adoption of targeted or lower-intensity AML-directed therapies, such as IDH inhibitors and venetoclax-based regimens. In our cohort, nearly all patients received ESA, frequently in combination with TPO-RA, and in selected cases, intravenous iron. Additional measures included vitamin K, antifibrinolytic agents, aggressive conservation of blood through micro draw protocols, and supplemental oxygen for symptomatic anemia. Notably, none of our patients died of major hemorrhagic complications. None of our patients received hemoglobin-based oxygen carriers or other blood substitutes.

Our case series highlights the importance of (i) individualizing leukemia-directed care, (ii) introducing blood substitutes, hemoglobin-based oxygen carriers, or agents that safely promote hematopoiesis without stimulating leukemogenesis, and (iii) proactively providing prophylactic thrombopoietic and erythropoietic support with myelosuppressive therapies (Figure 1). While strategies such as ESA, TPO-RA, intravenous iron, and antifibrinolytics can sometimes stabilize cytopenias and facilitate therapy, the overall prognosis of JW patients with acute leukemia and high-grade myeloid neoplasms remains poor, particularly in AML. Importantly, our series documents two ALL patients who successfully received intensive chemotherapy without transfusion support, underscor-

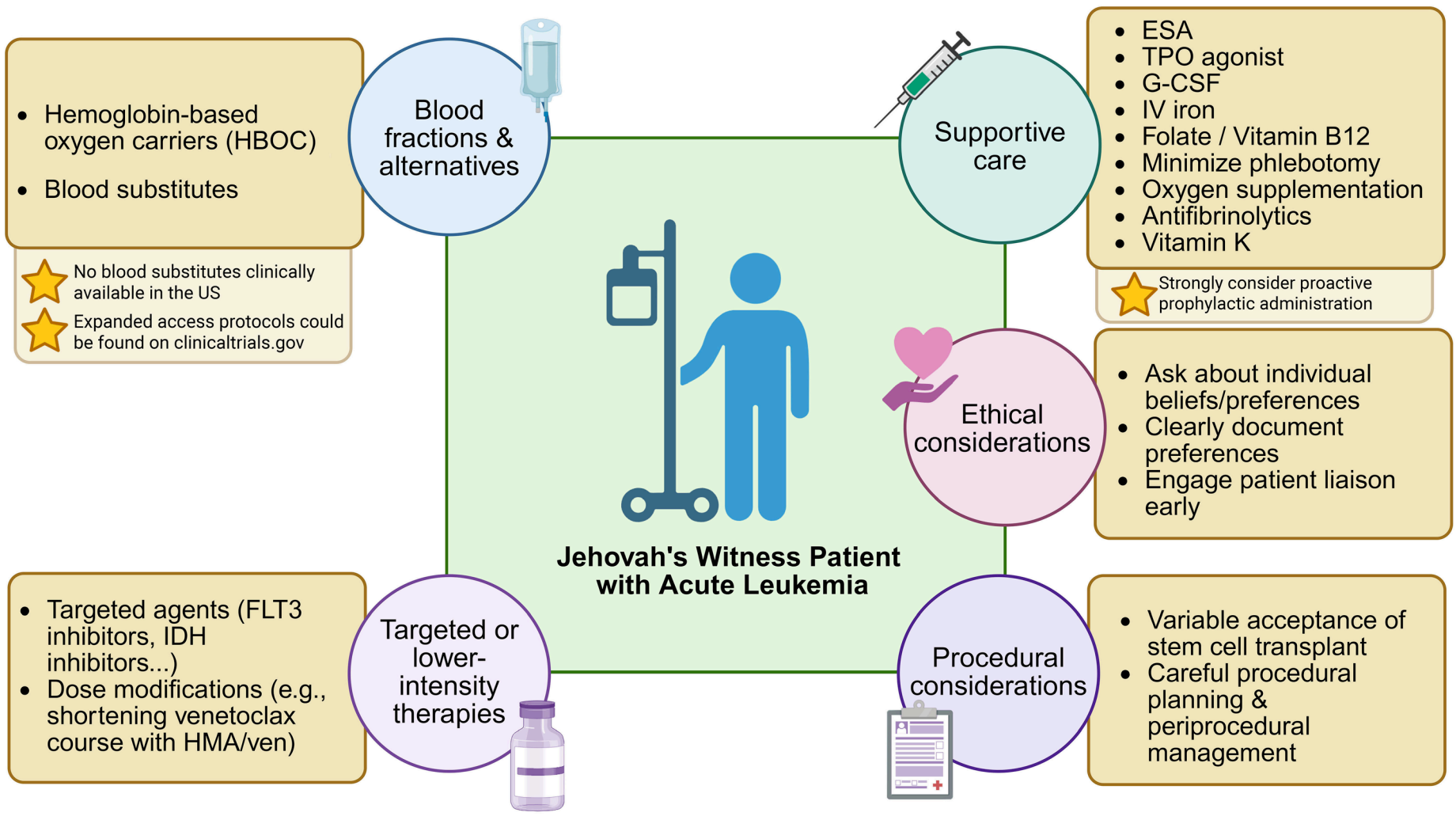

Figure 1. Integrated strategies for Jehovah's Witness patients with acute leukemia. HMA: hypomethylating factor; ven: venetoclax; ESA: erythropoiesis-stimulating agents; TPO: thrombopoietin; G-CSF; granulocyte colony-stimulating agents; IV: intravenous.

ing that such approaches are occasionally feasible with aggressive supportive care. For treating physicians, these cases highlight both the possibilities and the ethical dilemmas surrounding treatment decisions in patients who decline transfusions. Given the paucity of published data, our report adds practical insight into supportive measures and therapeutic outcomes that may help guide clinical decision-making in this challenging setting.

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Contributions

JZ and ANS conceived and designed the study, supervised data collection and analysis, and drafted and finalized the manuscript. JZ performed data collection and initial analysis. All other authors contributed to patient identification, data acquisition, and critical manuscript review. All authors approved the final manuscript.

Data-sharing statement

De-identified data are available from the corresponding author upon reasonable request and with appropriate institutional approvals.

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