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The treatment of acute lymphoblastic leukemia in Jehovah's Witnesses and patients who cannot accept blood products

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ABSTRACT

Jehovah's Witnesses cannot accept blood products based upon religious beliefs, and when they present with acute leukemia, the ideal treatment strategy can be controversial. We present six cases of Jehovah's Witnesses with acute lymphoblastic leukemia and show that complete remission can be achieved without using anthracycline in 83% (5/6) of patients. We also report, for the first time in this population, that the use of agents with novel mechanisms of action, such as blinatumomab and nelarabine, is associated with minimal myelosuppression and can produce durable responses, with 2 of 6 patients still alive in CR3 at 4.9 and 6.6 years.

1. Introduction

In 2018, the Jehovah's Witness denomination had over 8 million followers worldwide [1]. A characteristic belief of Jehovah's Witnesses (JW) is they do not accept blood products based upon interpretation of certain Bible verses [2]. This poses a clinical conundrum to medical professionals, especially when patients who identify with this religion present with medical issues that may require transfusion of blood products.

Blood transfusions are a key component of supportive care while treating patients with chemotherapy for acute leukemia. Additionally, it is common for a patient with acute leukemia to present with cytopenias that approach, or are already below, traditional transfusion thresholds. Without the ability to transfuse blood products, offering intensive chemotherapy proves difficult [3,4]. The care of JW presenting with acute leukemia can be challenging, but these patients can be offered chemotherapy with careful consideration to minimize transfusion requirements.

We summarize six cases (Table 1) of acute lymphoblastic leukemia (ALL) in JW from two institutions and present a review of the literature in an effort to demonstrate that these patients can be offered either intensive or reduced intensity chemotherapy with a particularly patient-tailored supportive treatment plan. We highlight two patients (Case 1 and Case 2) who were treated with newer agents (blinatumomab and nelarabine) and remain in remission to date. To our knowledge, this is the largest case series of ALL in JW.

2. Case 1

The patient is a 23-year-old man diagnosed with T-cell ALL. Cytogenetics by fluorescence in situ hybridization (FISH) showed loss of ETV6, and lymphoid molecular profile was negative. The patient received weekly vincristine 2 mg, prednisone 60 mg/m2 daily, and pegaspargase 2500 U/m2 on day 17. He received erythropoietin, romiplostim, iron sucrose, B12, and folic acid. Repeat marrow showed morphologic remission. He completed 24 months of POMP maintenance (6-mercaptopurine 150 mg daily, vincristine 2 mg monthly, methotrexate 20 mg/m2 weekly, and prednisone 200 mg day 1–5) but relapsed one year later. Given the duration of first remission, he began therapy again with weekly vincristine 2 mg, prednisone 60 mg/m2 daily, and pegaspargase 2500 U/m2 on day 18 with subsequent morphologic remission with recovery of blood counts. He was ineligible for stem cell transplant due to inability to receive transfusions. He completed two cycles of a modified dose Larson protocol: daunorubicin 30 mg/m2, cyclophosphamide 600 mg/m2, and pegaspargase 2500 U/m2 in cycle 1 and cyclophosphamide 600 mg/m2, cytarabine 75 mg/m2, and 6-MP 60 mg/m2 in cycle 2. Vincristine and pegaspargase were discontinued due to grade 3 anemia (nadir: 5.2 g/dl) and grade 4 thrombocytopenia. He relapsed after 20 months while on POMP maintenance when routine lumbar puncture showed CSF involvement of ALL and confirmed with

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bone marrow biopsy. The patient received high dose methotrexate (MTX) 3500 mg/m2 D1 and nelarabine 325 mg/m2 daily for five days. He achieved remission after 4 cycles. At the start of therapy with MTX and nelarabine, hemoglobin was 13.2 g/dL and platelets were 185 × 10^3/μL. Hemoglobin nadir with MTX and nelarabine was 10.8 g/dL and platelets 44 × 10^3/μL. He is now on maintenance per AALL0434 with POMP and nelarabine. He remains in CR3 for 18 months; 81 months from initial diagnosis.

3. Case 2

The patient is a 21-year-old man diagnosed with Ph negative B-cell ALL. Cytogenetics by FISH showed IGH re-arrangement, and lymphoid molecular profile showed SPEN mutation. He received vincristine 2 mg IV day 1, 8, 15, 28, dexamethasone 10 mg PO BID days 1–14, pegaspargase 2500 units/m2 IV on day 15 and supportive care with erythropoietin, iron sucrose, B12, folate, and romiplostim. Bone marrow biopsy on day 28 showed morphologic remission. The patient started intensification with MTX 3000 mg/m2 IV day 1, 15 and pegaspargase

Table 1
Patients who are Jehovah's Witnesses diagnosed with ALL treated with induction chemotherapy.

	Age, Sex	Diagnosis	Karyotype, Cytogenetics by FISH, Molecular studies	Treatment	Supportive agents	Overall treatment nadirs Hemoglobin (g/dL, Ref range 13.3–16.3) Platelet (x 10^3/μL, Ref range 140–400)	Response to induction	Outcome/ Duration of response
Case 1	23M	T-ALL	46, XY Loss of ETV6 None	Vincristine 2 mg weekly, Prednisone 60 mg/m2 D1–6, Pegaspargase 2500 U/m2 D17, IT Relapse 1: Vincristine 2 mg weekly, prednisone 60 mg BID D1–28, pegaspargase 2000 U/m2 D18, IT Cyclophosphamide, 600 mg/m2 D1 daunorubicin 30 mg/m2 D1, pegaspargase 2500 U/m2 D22 Cytarabine 75 mg/m2 D1–4 and D8–11, 6-MP 60 mg/m2 D1–14, cyclophosphamide 600 mg/m2 D1 Relapse 2: IT, HD MTX 3500 mg/m2, nelarabine 325 mg/m2	Erythropoietin, romiplostim, iron sucrose, B12, folic acid	5.2 18	CR	Alive 81 months
Case 2	21M	Ph(-) B-ALL	46, XY IGH rearrangement SPEN mutation	Vincristine 2 mg weekly, dexamethasone 10 mg BID D1–14, pegaspargase 2500 U/m2 D19, IT Consolidation: HD MTX 3 gm/m2, pegaspargase 2000 U/m2 (complicated by pancreatitis) Relapse 1: Blinatumomab 28 mcg/day CNS relapse: MTX 5000 mg/m2, IT MTX for six cycles, vincristine 2 mg weekly Relapse 2 (MRD+): Blinatumomab 28 mcg/day	Erythropoietin, romiplostim, iron sucrose, B12, folic acid	4.2 21	CR	Alive60 months
Case 3	44F	T-ALL	Complex karyotype MLL re-arrangement, loss of DEK Molecular data not available	Vincristine 2 mg, dexamethasone 40 mg weekly, IT	Erythropoietin, filgrastim, iron sucrose, B12	1.9 90	POD	Death Unknown date of death
Case 4	71F	Ph(-)B-ALL	46, XX IGH rearrangement, loss ETV6, loss of ABL1 PRDM1, SOCS1, TP53 mutations	Vincristine 2 mg weekly, rituximab 375 mg/m2 weekly, prednisone 60 mg/m2 daily, IT Cyclophosphamide, rituximab, prednisone (dosing unavailable) Relapse: Rituximab 375 mg/m2, dexamethasone 40 mg D1–4	Erythropoietin, filgrastim, iron sucrose, folic acid, B12, romiplostim, aminocaproic acid	6.8 3	CR	Death 6 months
Case 5	54F	Ph(-)B-ALL	46, XX IGH rearrangement None	Vincristine 2 mg weekly, prednisone 60 mg/m2 daily, pegaspargase 2500 U/m2 D17, IT	Erythropoietin, iron sucrose, folic acid, B12	2.4 12	CR	Death 2 months
Case 6	29F	Ph(-)B-ALL	46, XX FISH and molecular data not available	Vincristine 2 mg weekly, prednisone 60 mg/m2 daily, pegaspargase 2500 U/m2 D17, IT Cytarabine 75 mg/m2 D1–4, 6-MP 60 mg/m2 D1–4, pegaspargase 2500 U/m2 D15, rituximab 375 mg/m2 weekly (cytarabine discontinued for cytopenias) Relapse: Blinatumomab 9mcg with standard dose escalation to 28 mcg daily	Erythropoietin, iron sucrose, B12, folic acid, eltrombopag, hemopure	3.6 33	CR	Death 6 months

2500 units/m2 day 16, however had severe pancreatitis. The patient then began POMP maintenance. After one cycle, bone marrow biopsy showed relapsed disease. He received blinatumomab for 2 cycles, and restaging marrow showed morphologic and cytogenetic remission. Hemoglobin and platelets at the start of therapy were 12.9 g/dL and 124 $\times$ 10^3/μL respectively. Treatment nadirs during blinatumomab were hemoglobin 10.9 g/dL and platelets 99 $\times$ 10^3/μL. The patient resumed POMP maintenance, however after seven cycles had relapse in CSF. He received high dose MTX 5000 mg/m2, IT MTX for six cycles, vincristine 2 mg weekly for four doses according to AALL1131 Interim Maintenance. Follow up bone marrow biopsy showed morphologic remission, however minimal residual disease positivity. He received blinatumomab for 4 cycles and craniospinal radiation. During treatment with blinatumomab, the patient had normal hemoglobin levels and grade 1 thrombocytopenia. The patient remains in CR3 for 28 months; 60 months from initial diagnosis.

4. Discussion

Traditional induction regimens for acute leukemia are myelosuppressive by nature and require prolonged monitoring of patients' blood counts and adverse events during administration. Patients undergoing induction for acute leukemia receive approximately 8–10 units of red blood cells and 8 units of platelets [5]. Our series shows that remission can be achieved without transfusions utilizing a vincristine, prednisone, and pegaspargase treatment backbone. Anthracycline can be included at reduced dosing or added at a later point when blood counts allow. The treatment of acute leukemia in Jehovah's Witnesses forces hematologists to re-think traditional transfusion guidelines since patients cannot accept blood products. Also, supportive care with products such as erythropoietin, colony stimulating factors, and anti-fibrinolytics are important considerations.

We present six JW treated for ALL at our institution. None accepted blood products. All were induced with a modified version of the ECOG2993 protocol without anthracycline. All but one patient, who possessed complex karyotype, obtained a morphologic remission after induction; one patient died of complications related to treatment with pegapaspargase. Two patients died due to relapsed disease. Two patients remain alive in third remission. At first relapse, case 1 was re-induced with the same regimen and at second relapse nelarabine was added. Now the patient remains in remission on maintenance therapy 81 months after diagnosis. Case 2 was treated with blinatumomab at first relapse and again for MRD+ relapse, and this patient remains in remission 60 months after diagnosis. Overall, two patients were treated with blinatumomab for relapsed disease. One patient died from cytokine release syndrome despite administration of tocilizumab, perhaps related to high disease burden. No patients had bleeding complications.

Less than 50 cases of acute leukemia in JW have been reported in the literature [6], only 12 of which are ALL. For the purpose of this discussion, we will review JW patients with ALL. The use of anthracycline can be controversial due to myelosuppression, however 11 of the 12 patients reviewed had either doxorubicin or daunorubicin during induction, some at reduced dosing. Ten patients achieved CR with induction. Four patients relapsed, of which 3 died, one of whom received salvage chemotherapy. Little is reported about the salvage regimens [4,7]. At the time of these patients' relapses, blinatumomab was not yet available. Blinatumomab now serves as an option for salvage therapy and is particularly appealing for JW due to its minimal rate of myelosuppression. Of 116 patients treated with blinatumomab, only 1–3% of patients experienced grade 3 or 4 anemia or thrombocytopenia [8]. Inotuzumab ozogamicin is also approved for relapsed or refractory setting for patients with ALL, however the rate of thrombocytopenia may limit its use in this population.

In our series, the majority of patients had an overall treatment nadir considered critically low. Four out of six patients had hemoglobin nadirs of <5 g/dL (Table 1). Patients were given supportive care with B12, folate, erythropoiesis stimulating agents, thrombopoietin receptor agonists, anti-fibrinolytics, and granulocyte colony stimulating factors. The use of the aforementioned medications has been well documented during induction chemotherapy for acute leukemia [6,9–14]. NCCN guidelines for JW with acute myeloid leukemia also support the use of such agents, and though no such guidelines formally exist for ALL, these supportive measures should be discussed with and offered to all Jehovah's witnesses who will undergo myelosuppressive chemotherapy. Supportive care recommendations for JW undergoing autologous stem cell transplant has been previously published [15]. For our patients with critically low blood counts, similar supportive care was implemented. Patients were encouraged bed rest to limit physical exertion and daily labs were avoided unless clinically indicated. Labs were collected in pediatric tubes. Another consideration would be the use of hormonal agents or an intrauterine device for menstruating women to mitigate blood loss.

5. Conclusion

Though the literature suggests that full or reduced dose anthracycline during induction can be used in JW, we highlight durable remissions can be achieved without anthracycline, particularly if the hemoglobin or platelet count at diagnosis precludes its use. If anthracyclines are used, lower doses should be considered in addition to intensifying non-myelosuppressive agents. Many adults who achieve remission will relapse. We show that relapsed JW ALL patients can be salvaged with more novel agents, such as blinatumomab and nelarabine, which do not require the same level of transfusion support as other regimens. Future directions for these patients should include using these agents in the frontline setting, combined with non-cytotoxic agents and reduced doses of chemotherapy to minimize toxicity and obtain durable remissions.

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Ethics approval

IRB exemption was granted per HSRO.

Patient consent

The patients who are living were treated with standard of care as per physician discretion and were retroactively consented to be a part of this review.

CRediT authorship contribution statement

Nina Nguyen: Conceptualization, Data curation, Investigation, Project administration, Visualization, Writing – original draft. **Ellen Madarang:** Conceptualization, Data curation, Investigation, Project administration, Visualization, Writing – review & editing. **Alvaro Alencar:** Investigation, Project administration, Supervision, Visualization, Writing – review & editing. **Justin Watts:** Conceptualization, Investigation, Project administration, Supervision, Visualization, Writing – review & editing. **Terrence Bradley:** Conceptualization, Investigation, Project administration, Supervision, Visualization, Writing – review & editing.

Declaration of Competing Interest

JW: Bristol Myers Squibb: Consultancy; Takeda: Consultancy, Research Funding; Immune Systems Key, Ltd: Research Funding; Rafael Pharmaceuticals: Consultancy; Reven Pharmaceuticals: Consultancy.

AA: Seattle Genetics: Consultancy; Kite Pharma: Consultancy. Karyopharm: Consultancy; Janssen: Consultancy; Incyte: Consultancy; Epizyme: Consultancy; Celgene: Consultancy; BeiGene: Consultancy; Amgen: Consultancy. TB: Novartis: Speakers Bureau, Advisory Board; AbbVie: Speakers Bureau, Advisory Board.

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