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Outcomes of Jehovah's Witnesses with hematological malignancies treated without transfusions — single center experience

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Abstract: Malignancies of the hematopoietic system frequently are associated with severe cytopenias requiring transfusions of blood components. Refusal of blood components by Jehovah's Witnesses (JW) produces challenges to treatment. In this report we describe the outcome of hematological malignancies of JW patients treated without transfusions. Altogether, eight JW, diagnosed 1994–2015, 6 (75%) females, the median age at diagnosis 40 years (range, 20–78), were included into the analysis. The diagnoses were: acute lymphoblastic leukemia (2, 25%), acute myeloid leukemia (2, 25%), non-Hodgkin's lymphomas (4, 50%). One patient died without treatment while the remaining 7 patients received treatment, including imatinib in 1 patient with *BCR-ABL1*+ acute lymphoblastic leukemia. Five (62.5%) patients received erythropoiesis stimulating agents. Median hemoglobin concentration at diagnosis was 8.7 g/dL (range, 6.3–13.1), and it decreased to 3.2 g/dL (range, 2.6–9.3) during first-line treatment. Median platelet count at diagnosis was 52×10^9/L (range, 15–392). All patients became thrombocytopenic upon treatment reaching median platelet count 8×10^9/L (range, 2–85). Five patients developed respiratory failure. Anemia contributed substantially to the death of 3 out of 6 patients (50%). One patient (17%) developed central nervous system bleeding in the course of thrombocytopenia. Objective response rate was 43%, with 29% complete remissions after first-line treatment. Despite the median overall survival of 15.3 months (95% CI, 0.2–52.2), all but one acute leukemia patients succumbed shortly after the diagnosis. To conclude, the outcome of JW treated because of hematological malignancies without blood transfusions is very dismal, nevertheless, selected patients can obtain complete remissions. Anemia contributes significantly to the death of JW.

Keywords: Jehovah's Witnesses, leukemia, lymphoma, blood transfusion, platelet transfusion.

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Introduction

Cytopenias are frequently encountered in malignancies of the hematopoietic system. They are mainly due to neoplastic infiltration of the bone marrow and the negative impact of cytokines produced by the leukemic/lymphomatous cells on proliferation and survival of the committed precursors [1, 2] and not to the shortage of endogenous growth factors e.g., erythropoietin. Additionally, they can be substantially aggravated by chemotherapy used to treat these disorders. To overcome the risks associated with their occurrence, cellular blood components, such as packed red blood cells and platelet concentrates are used to correct anemia and thrombocytopenia, respectively [3–5]. Jehovah's Witnesses, because of their belief, consistently refuse to receive these blood components, while they allow for the usage of growth factors, and among them erythropoiesis stimulating agents (ESAs). However, stimulation of erythropoiesis can only be effective when the detrimental effects mentioned above i.e., neoplastic infiltration of the bone marrow and the negative impact of cytokines are not active and there is a space in the bone marrow to produce red blood cells. Furthermore, cells of hematopoietic malignancies may by themselves possess erythropoietin receptors and be stimulated by ESAs. According to the international guidelines, ESAs should be used very cautiously in malignancies treated with curative intent because of the increased risk of premature death or progression upon the use of ESAs in patients with cancer [3, 6].

Diagnosis of malignancy of hematopoietic system in Jehovah's Witness is a challenge to contemporary therapeutic methods. First, the available evidence is limited [7–12]. No guidelines exist and each patient is treated individually depending on the center's experience, and some centers even do refuse to treat such patients [7].

Here we report our 20-year experience with JW to provide more data to better treat these patients.

Materials and Methods

The medical files of Jehovah's Witnesses who consistently refused to receive any blood and platelet transfusions were analyzed retrospectively for the type of the underlying hematological malignancy, the type of therapy used, the presence and magnitude of cytopenias before and after treatment, treatment strategies used to overcome cytopenias, the effect of cytopenias i.e., anemia and thrombocytopenia on survival, and finally overall survival. While it is allowed to use granulocyte colony stimulating factors in Jehovah's Witnesses, neutropenia was not the subject of this analysis.

All patients received supportive treatment, including prevention of tumor lysis syndrome, and prophylactic antibacterial, antifungal, and antiviral drugs, according to local standards. Blood tests during nadir were performed the least frequently as possible, in order not to aggravate already existing life-threatening anemia.

The study received Institutional Review Board approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Statistical analysis

Continuous variables were summarized using median (range), while frequency tables were used for categorical variables. The primary endpoint was the occurrence of life-threatening anemia and thrombocytopenia. Secondary endpoints were response rate, including objective response rate (ORR) and complete response (CR), and overall survival (OS), estimated by the Kaplan-Meier method. OS was calculated solely for patients receiving any form of antineoplastic therapy. All calculations were performed with the use of SAS 9.2 System for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patients

Eight Jehovah's Witnesses patients diagnosed between 1994 and 2015 were identified. All but one patient required treatment at diagnosis. The patient diagnosed with marginal zone lymphoma (initially diagnosed as chronic lymphocytic leukemia) started therapy 2 years after the diagnosis. One acute myeloid leukemia (AML) patient died without starting induction chemotherapy after having been discharged home on the patient's own demand.

At the time of diagnosis 6 out of 8 patients (apart from the patient diagnosed with marginal zone lymphoma and the patient with diffuse large B-cell lymphoma (DLBCL)) were already anemic. Median concentration of hemoglobin was 8.7 g/dL (range 6.3–13.1), which decreased to 3.2 g/dL (range 2.6–9.3) during first-line treatment. The patient with marginal zone lymphoma did not develop anemia during first-line chemotherapy, however, the patient developed extremely severe anemia upon disease progression with a hemoglobin concentration of 2.2 g/dL. Five patients (62.5%) were treated with erythropoiesis stimulating agents, none received iron supplementation or anti-fibrinolytic drugs.

Median platelet count at diagnosis was 52×10^9/L (range 15–392), thrombocytopenia was present in 5 patients. The patient with marginal zone lymphoma did not develop thrombocytopenia during first-line chemotherapy, however, this patient developed it during the progression of the lymphoma, with the lowest platelet count of 3×10^9/L. All other patients were thrombocytopenic during treatment/follow up — median PLT count 8×10^9/L (range 2–85).

Exact data on the magnitude and duration of anemia and thrombocytopenia are presented in Table 1.

Table 1. Characteristics of Jehovah's Witnesses patients

Abbreviations:

6-MP	—	6-mercaptopurine
A1 according to GMALL	—	A1 chemotherapy block according to **German** Multicenter Study Group for Adult ALL
ALL	—	acute lymphoblastic leukemia
AML	—	acute myeloid leukemia
CLB	—	chlorambucil
CNS	—	central nervous system
CNVP	—	cyclophosphamide, mitoxantrone, vincristine, prednisone
DA5	—	cytarabine, daunorubicine (2 + 5)
DLBCL	—	diffuse large B-cell lymphoma
F	—	female
HDMP	—	high-dose methylprednisolone
Hgb	—	hemoglobin
i.t.	—	intrathecal
M	—	male
MZL	—	marginal zone lymphoma
NA	—	not applicable
OS	—	overall survival
PALG ALL6	—	Polish Adult Leukemia Group acute lymphoblastic leukemia 6
PDN	—	prednisone
PMLCL	—	primary mediastinal large cell lymphoma
PLT	—	platelet
R-CHOP	—	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-CVP	—	rituximab, cyclophosphamide, vincristine, prednisone
RT	—	radiotherapy
VCR	—	vincristine

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Patient	Sex	Age	Diagnosis	Bone marrow involvement at diagnosis	First line treatment	Treatment of relapse/ progression	Hgb at diagnosis (g/dL)	The lowest Hgb (g/dL)	Days with Hgb <6 g/dL during first-line treatment	Days with Hgb <6 g/dL during treatment of relapse	PLT at diagnosis ($\times 10^9$/L)	The lowest PLT ($\times 10^9$/L)	Days with PLT <10 × 10^9/L during first-line treatment	Days with PLT <10 × 10^9/L during treatment of relapse	Death	OS (months)	Anemia contributing to death	Cause of death
#1	M	56	ALL	blasts: 37%	Palliative (VCR; PDN; 6-MP)	Palliative (VCR; PDN; 6-MP)	7.7	2.6	50	5	15	2	0	17	yes	4.2	yes	septic shock, multiorgan failure
#2	M	39	ALL *BCR-ABL1+*	blasts: 94%	PALG ALL6 (incl. imatinib)	i.t.; imatinib	8.3	2.6	≥28	0	17	4	≥8	0	no	20.1	NA	NA
#3	F	20	AML	blasts: 59%	no treatment	NA	6.3	5.2	≥4	NA	20	13	NA	NA	yes	0.8	missing data (death at home)	missing data (death at home)
#4	F	25	AML	unknown	DA5	NA	10.9	3.0	2	NA	49	3	3	NA	yes	0.2	no	CNS bleeding
#5	F	73	DLBCL	not done	Only prephase (PDN, HDMP)	NA	6.3	3.3	17	NA	55	28	0	NA	yes	0.5	yes	multiorgan failure, tumor lysis syndrome
#6	F	42	MZL	not done	CLB; Cladribine	CHOP + CNVP	13.0	2.2	0	54	>150	3	0	14	yes	52.2	yes	multiorgan failure
#7	F	78	DLBCL	lymphocytes: 30%	R-CVP	R-CVP	9.0	9.3	0	0	110	85	0	0	yes	15.3	unknown	unknown
#8	F	37	DLBCL (PMLCL)	no involvement	A1 according to GMALL; R-CHOP +i.t.	RT	13.1	5.4	3	0	110	7	3	0	no	10.6	NA	NA

Case 1

A 56-year old man was admitted to the hospital because of marked fatigue and weight loss. His complete blood count test revealed pancytopenia, with a hemoglobin concentration of 7.7 g/dL, PLT count of 15×10^9/L, and neutrophils of 0.66×10^9/L. After bone marrow examination he was diagnosed with B-cell acute lymphoblastic leukemia, not otherwise specified. Palliative treatment with prednisone 1 mg per kg bodyweight along with vincristine 2 mg per dose (a total of 5 doses) was initiated. Despite ESAs treatment, the patient developed severe anemia with hemoglobin concentration below 6 g/dL lasting for 50 days, including 25 days with hemoglobin concentration below 3.5 g/dL. The lowest hemoglobin concentration reached 2.6 g/dL. At that time, he required oxygen supplementation. After the recovery of blood counts, the patient started consolidation treatment with 6-mercaptopurine. However, only after a month, an increased blast count (24.4%) was found in the bone marrow, as well as intensive infiltrations were depicted within bones by magnetic resonance imaging, performed because of severe bone pain resulting in disability. An attempt was made to administer prednisone 1 mg per kg bodyweight again along with vincristine 2 mg per week and 6-mercaptopurine 50 mg per dose, nevertheless, the patient succumbed to septic shock with severe respiratory failure caused by both infection and severe anemia. His hemoglobin concentration directly antecedent to death was 3.9 g/dL, his platelet count — 2×10^9/L.

Case 2

39-year old male patient with a history of fever, easy bruising, and bone pain, was diagnosed with acute lymphoblastic leukemia, *BCR-ABL1*+. At diagnosis his blood parameters were as follows: hemoglobin concentration 8.3 g/dL, PLT 17×10^9/L. Reduced doses of standard induction chemotherapy according to PALG ALL6 protocol (Polish Adult Leukemia Group acute lymphoblastic leukemia 6) were used i.e., vincristine 2 mg once weekly for 4 weeks, daunorubicin 30 mg per meter square week 3 and 50 mg per meter square week 4, prednisone 1 mg per kg body weight, imatinib initially 400 mg and eventually 600 mg per day continuously. The treatment was complicated by an aggravation of cytopenias with hemoglobin concentration below 6 g/dL lasting at least 28 days, including at least 11 days with hemoglobin concentration below 3.5 g/dL, and the lowest hemoglobin concentration of 2.6 g/dL. The lowest platelet count was 4×10^9/L. At that time the patient complained of fatigue, signs of skin and mucosal bleeding diathesis; on physical examination tachycardia was present. Oxygen therapy was used, as well as ESAs were administered. Treatment resulted in complete response. After hematopoietic recovery, the patient continued with consolidation and further maintenance treatment combined with imatinib according to

PALG ALL6. Unfortunately, after 18 months of CR the patient developed neurological symptoms. Cerebrospinal fluid examination revealed the presence of leukemic blasts shortly before writing this report.

Case 3

20-year old female patient with a history of easy bruising and fatigue was diagnosed with acute myeloid leukemia. At the time of diagnosis, she was both anemic (Hgb 6.3 g/dL) and thrombocytopenic (PLT 20 × 10^9/L), and these parameters further declined during the next days of hospital stay. The patient did not receive any treatment. She was discharged on her demand and died shortly thereafter.

Case 4

25-year old female patient was diagnosed with acute myeloid leukemia. The presenting syndromes were fatigue, fever, and tonsillitis. At diagnosis her complete blood count parameters were as follows: hemoglobin 10.9 g/dL, platelet count 49 × 10^9/L. She received antibiotics along with induction treatment according to reduced DA protocol (cytarabine 100 mg per meter square days 1 through 5, daunorubicin 45 mg per meter square days 1 through 3). Despite reduced doses of chemotherapy and ESAs use, the treatment resulted in aggravation of anemia to 3 g/dL and thrombocytopenia to 3 × 10^9/L. The patient died because of central nervous system hemorrhage 2 days after completion of induction treatment.

Case 5

73-year old female patient complaining of fatigue and resting dyspnea was diagnosed with a leukemic phase of diffuse large B-cell lymphoma. At diagnosis her complete blood count parameters were as follows: hemoglobin 6.3 g/dL, platelet count 55 × 10^9/L, white blood cells 45 × 10^9/L. Already at diagnosis she had a spontaneous tumor lysis syndrome. As a prephase treatment steroids were used (prednisone, and afterward high-dose methylprednisolone). The patient developed multiorgan failure and died after the first dose of high-dose methylprednisolone, due to both anemia and underlying disease.

Case 6

42-year old female patient was diagnosed initially with chronic lymphocytic leukemia in another hematological center, where she received sequentially chlorambucil and cladribine. Upon admission to our department after reexamination, the revision of an

initial diagnosis was performed, and eventually marginal zone lymphoma was diagnosed. Because of disease progression, the patient received treatment according to CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) and further CNOP (cyclophosphamide, vincristine, mitoxantrone, and prednisone) protocols. Severe anemia developed with marked dyspnea, heart palpitation, and chest pain. ESAs were administered, oxygen therapy was used. Despite treatment, the patient died with a hemoglobin concentration of 2.2 g/dL and a platelet count of 3×10^9/L.

Case 7

78-year old female patient was diagnosed with diffuse large B-cell lymphoma, clinical stage IV. Her hemoglobin concentration at diagnosis was 9 g/dL, PLT count 110×10^9/L. Treatment with R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) was initiated. The patient obtained complete remission, however after half a year she experienced disease relapse. At that time the patient refused also to receive cytostatic agents producing alopecia, therefore R-CVP was used again. After 3 cycles the patient was lost to follow-up. She died at home of an unknown cause 2 months later.

Case 8

37-year old female patient was admitted to our department because of primary mediastinal B-cell lymphoma. The patient complained of chest pain, cough, and general symptoms. At diagnosis she was neither anemic nor thrombocytopenic, however already before the start of chemotherapy she experienced moderate anemia (Hgb 9.6 g/dL). Chemotherapy according to German Multicenter Study Group for Adult ALL (GMALL) protocol was initiated, which resulted in prompt anemization, aggravated by menstrual bleeding. The lowest Hgb concentration was 5.4 g/dL. The patient suffered from dyspnea requiring oxygen support. ESAs were administered. After an increase of hemoglobin concentration, the patient continued less aggressive treatment according to R-CHOP protocol. Despite a good interim response, the final response was a progressive disease, and the patient was qualified for salvage radiotherapy with the result of partial remission. After 10.6 months the patient remains alive.

Response. Survival analysis. Impact of cytopenias on survival

Summarizing these short case reports, the objective response rate for treated patients reached 42.9%, with 28.6% complete remissions (CR) after first-line treatment. Two patients are alive at the time of this report: one ALL *BCR-ABL1*+ patient, who has just relapsed within the central nervous system (CNS), and one DLBCL patient. All other

patients succumbed. The survival time of the patients is provided in Table 1. Very severe anemia (median concentration 3.6 g/dL, range 2.2–3.9 g/dL) contributed to the death of three out of six (50%) deceased patients by induction of respiratory insufficiency and finally development of multiorgan failure. In one patient thrombocytopenia resulted in a hemorrhagic stroke (17%).

Discussion

In this report, we describe results and difficulties arising in Jehovah's Witnesses diagnosed with either acute leukemias or lymphomas who refuse to receive any blood components independently of circumstances. Although we describe a heterogeneous group of patients, it can be easily noted, that majority of patients, similarly as in other reported small series of patients [7, 10, 12] received "reduced intensity" treatment due to the risk of severe myelosuppression, which resulted in a very low objective response rate of only 42.9% (28.6% complete remissions). Unlike Mazza *et al.* [9] who reported a response rate of 100% for AML patients, both we and others [7, 12] obtained much worse results. On contrary to others, we also did not observe very long-lasting complete remissions in ALL patients [7]. The longest CR (18 months) obtained in our study was in a patient diagnosed with *BCR-ABL1*+ acute lymphoblastic leukemia, who received imatinib in addition to chemotherapy. This patient eventually developed disease progression with central nervous system involvement. In our study, no patient was eligible for hematopoietic stem cell transplantation, unlike in the study of Ford [13], where patients after ESAs preparation were subjected to high dose chemotherapy with autologous hematopoietic stem cell support. In comparison to others [7], we observed a substantial proportion of early deaths occurring already during induction or even prephase treatment. This was probably due to the fact, that majority of patients had been diagnosed with advanced disease.

Even though less myelotoxic regimens (i.e., R-CVP instead of R-CHOP or R-CHOP instead of GMALL) or reduced dosing regimens were used, both severe anemia and thrombocytopenia were observed. Hemoglobin concentration decreased to 3.2 g/dL (range 2.6–9.3), while platelet count to 8×10^9/L (range 2–85) during the first-line treatment. Our results are slightly worse than the results reported by Laszlo *et al.* [7] and much worse than results reported by Brown, where the lowest hemoglobin concentration reached 6.8 g/dL (range 3.6–7) [10]. In our group cytopenias contributed substantially to the death of JW — in fact, at least 4 out of 6 deceased patients died because of severe cytopenia (all suffered from severe anemia, while 1 patient additionally developed a CNS hemorrhage), similarly to in the report of Cullis *et al.*, where 2 out of 3 patients treated without transfusions succumbed to anemia [11].

In our group, five patients (62.5%) received erythropoiesis stimulating agents. The patients who did not receive ESAs, either died very shortly after the diagnosis or did not develop severe anemia during the treatment. As it was found in other reports and has been confirmed by our study, the use of ESAs is able to reverse anemia only if the patient lives long enough [14], which is not the case for the significant proportion of acute leukemia patients.

There are reports of single cases in the literature on the use of less myelotoxic drugs i.e., azacitidine [15, 16] and gemtuzumab ozogamicin [17, 18] alone or in combination with "reduced intensity" standard chemotherapy, showing the beneficial outcome. Although these drugs may be an alternative option for these patients, larger series are missing showing the real efficacy of these drugs. Similarly, although effective in single cases [19], more data is needed on the use of alternative oxygen-carriers.

To conclude, treatment of Jehovah's Witnesses is extremely challenging, especially if they are diagnosed with rapidly progressing and aggressive disease, and when the treatment of choice encompasses myelosuppressive drugs. The prognosis of such patients is very dismal with short overall survival. Severe cytopenias, and especially anemia contribute substantially to the death of the affected patients. There is a need to explore alternative supportive measures for these patients as well as alternative treatment protocols. Before any reliable data is available, very thorough patient counseling before starting the treatment is necessary.

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Conflicts of interest

None declared.

Authors' individual contributions

J.D.-S.: Conceptualization, Methodology, Investigation, Data curation, Software, Writing-Original draft preparation; A.W.-G.: Conceptualization, Writing-Reviewing, and Editing; J.D.-T: Conceptualization, Writing-Reviewing, and Editing; A.W.: Inves-

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