Asian Hematology Research Journal

4(4): 34-43, 2021; Article no.AHRJ.70444

Management of Severe Aplastic Anaemia in a Jehovah's Witness patient: The challenge and Lessons

Nelson I. Oguanobi[1,2*], Augustine N. Duru[3,4], Paul C. Okorie[5] and Amobi O. Egwuonwu[6,7]

[1]Department of Internal Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria.
[2]Department of Pharmacology and Therapeutics, Faculty of Medical Sciences, University of Nigeria, Enugu Campus, Nigeria
[3]Department of Haematology, University of Nigeria Teaching Hospital Enugu, Nigeria.
[4]Department of Haematology, Faculty of Medical Sciences, University of Nigeria, Enugu Campus, Nigeria
[5]Department of Radiology, Enugu State University Teaching Hospital, Parklane, Enugu, Nigeria
[6]Department of Surgery, Nnamdi Azikiwe University Teaching Hospital Nnewi, Anambra State, Nigeria.
[7]Department of Surgery, Faculty of Medicine, Nnamdi Azikiwe University Nnewi Campus, Anambra State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Juan Carlos Troiano, University of Buenos Aires, Argentina.
Reviewers:
(1) Susumu Inoue, Michigan State University, United States.
(2) Dito Anurogo, Universitas Muhammadiyah Makassar, Indonesia.
Complete Peer review History: https://www.sdiarticle4.com/review-history/70444

Original Research Article

Received 15 May 2021
Accepted 20 July 2021
Published 22 July 2021

ABSTRACT

Aplastic anaemia is a life threatening consequence of severe bone marrow failure often requiring supportive care with component blood transfusions and stem cell replacement procedures. In this case report and review of literature, the authors highlight peculiar challenges in the management of severe aplastic anaemia in patients with strong objection to blood transfusion. The impact of optimal use of blood transfusion alternative pharmacological strategies on clinical outcome indices is

**Corresponding author: E-mail: nelson.oguanobi@unn.edu.ng, nelsonoguanobi@gmail.com;*

evaluated and relevant lessons in the management of this unique category of patients in poor resource environments are learned.

Keywords: Aplastic anaemia; jehovah's witnesses; transfusion-alternatives; challenges; lessons.

1. INTRODUCTION

Aplastic anaemia is a heterogeneous disorder characterized by peripheral pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin [1]. The majority (70–80%) of these cases are categorized as idiopathic because their primary aetiology is unknown. In approximately 15–20% of patients, the disease is either constitutional/inherited or acquired. Inherited aplastic anaemia is caused by gene defects, and is most common in children and young adults and is associated with increased risk of development of leukaemias and other malignant and somatic disorders [1,2]. Acquired aplastic anemia which is more common in adults is attributed to immune mediated insult and destruction of hematopoietic stem-cells secondary to viral infections, toxic chemicals, chemotherapy and radiations [1].

Transfusions of cellular blood components, among other measures, are the recommended emergency supportive care in management of patients with life threatening anaemia[1]. However, the transfusion option is absolutely unacceptable to Jehovah's Witnesses patients for religious reasons [3,4,5]. This stance can present significant challenge to health care professionals especially in resource poor developing countries where access to modern intensive care facilities is limited. In this article, we share our experiences in the management of a 49year old Jehovah's Witnesses patient with severe aplastic anaemia in a resource limited setting. Relevant literatures that highlight useful strategies in addressing the challenges in management of this category of patients are also reviewed.

2. CASE SUMMARY

Mr. A.Z is a 49-year old male Nigerian school teacher who presented with a three month history of fever, malaise, and progressive weakness. The fever was insidious in onset, high grade, continuous and associated with chills and rigor. There was neither yellowness of the eyes nor change in normal urine colour or volume. He had not experienced any body itching, drenching night sweats, sore throat, cough, dyspnoea, loss of taste or smell sensations. There was no history of exposure to toxic chemicals, herbicides, and pesticides.

He initially sought medical attention with a primary care physician who placed him on antimalarial drugs (Arthemeter/Lumefantrime 80/480mg twice daily for 3days) and antibiotics (tablets Ciprofloxacin 500mg twice daily(bd) for 10 days and later tablets Amoxycilline/Clauvulanic acid 625mg bd for 7days). However, his condition continued to deteriorate. The fever remained unabated and he became progressively weak prompting the referral to our health facility. On clinical evaluation, he was fully conscious, febrile (temperature 39.2^0Celsius), severely pale and lethargic but had no jaundice, digital clubbing, leg oedema or enlarged peripheral lymph nodes. His body weight was 70Kg and body mass index 23.9. He had tachycardia (heart rate = 106/minute), tachypnoea (Respiratory rate=38/minute) and normal blood pressure (120/70mmHg supine). Other systemic examination revealed essentially normal findings. Accompanying laboratory investigation results (from referring hospital) done 6 days earlier showed haemoglobin (Hb) 7g/dl, white blood cell count (WBC) 1.2 x 10^9/L, Platelet count 114 x 10^9/L. A repeat blood count revealed Hb 4.2g/dl, WBC 2.41 x 10^9/L, Platelet count 112 x 10^9, a reticulocyte count of 1% (0.014 x 10^9/L) and erythrocyte sedimentation rate 150mm 1^{st} hour (Westergreen). Details of the laboratory results are presented in Table 1. A working diagnosis of sepsis on a background severe aplastic anaemia of unknown aetiology was made.

The diagnosis and treatment options were clearly explained to the patient to his understanding. However, he politely but firmly objected to transfusion of blood and blood products. His decision was clearly stated in a signed irrevocable durable power of attorney form, which was witnessed and attested to by two reliable persons.

He was commenced on the following treatment:

Intravenous (IV) Meropenem 1g 12 hourly, IV Metronidazole 500mg 8 hourly, Intranasal 100%

oxygen continuously at flow rate of 4Litres/minute maintaining oxygen saturation ($SPO_{2)}$ between 98-100%.

Subcutaneous Human recombinant Erythropoietin alfa 12,000 International Units (I.U) alternate days along with IV Iron dextran 200mg in 500ml Normal Saline at 10 drops/minute (after a test dose of IV 25mg). Iron dextran infusion was continued daily until the calculated total dose of 2,750mg (based on lean body weight and haemoglobin deficit) was reached.

Tabs Vitamin C 200mg tds (thrice daily), Tabs. Multi-vitamin B complex 2 tds (containing the B vitamins: B1 (thiamin 10mg) , B2 (riboflavin 5mg) , B3 (niacin 15mg), B5 (pantothenic acid 5mg), B6 (pyridoxine 2mg), B7 (biotin 0.03mg), B9 (folate 0.4mg), and B12 (cobalamin 0.003mg).

By the third day of admission, fever had started to subside, but the haemogram had dipped to its nadir level of 3.0g/dL.

A consultant Haematologist reviewed the patient, examined the peripheral blood film and performed a trephine bone marrow aspiration biopsy, and the specimen were sent for laboratory investigation. The blood film showed marked erythrocytopenia with normochromic normocytic red cells. There were occasional hypochromic cells with mild anisopoikilocytosis. There were marked leucocytopenia with small to medium-sized mononeuclear cells as well as some dysplastic cells. There were also marked thrombocytopenia with occasional giant forms. The result of the bone marrow biopsy evaluation revealed: marked hypocellular marrow fragment and trail (myeloid: erythroid M:E ratio =1:1) with reduced erythroid activity. Myelopoiesis was markedly reduced with maturation arrest. There was preponderance of large myeloblast cells having deeply basophilic granular cytoplasm with Auer rods, round nuclear outline, and open nuclear chromatin pattern. Detailed bone marrow findings are presented in Table 2. The bone marrow features were suggestive of bone marrow failure secondary to acute myeloblastic leukaemia (French-American-British FAB- M2),-{to rule out myelophthisic anaemia}. Blood cultures and viral studies (Hepatitis B, Hepatitis C, HIV, Lassa fever and COVID-19 screening) were all negative. Chest X-ray and abdominopelvic ultrasound examinations showed normal findings. Results of serum electrolytes, urea, creatinine and liver function tests were all within normal limits.

The following were added to the treatment regimen:

Filgrastim, a granulocyte colony-stimulating factor (G-CSF) 300mcg given subcutaneously daily, Tab. Eltrombopag 50mg daily and IV Vincristine 1.4mg/m^2 weekly.

By the 5^{th} day of admission, the body temperature had returned to normal. The patient was maintained on continuous intranasal oxygen support with regular monitoring of oxygen saturation status. The haemoglobin level improved gradually and steadily by approximately 1.3 gram weekly from 4g/dL (by the 3^{rd} week of admission) to 9.1g/dl four weeks after. The reticulocyte count also increased from 1.0% on admission to 2.3%. There were also significant improvements in the leucocyte and thrombocyte counts (Table 1). He was subsequently weaned off oxygen therapy and is currently being evaluated for possible bone marrow transplant procedure.

Table 1. Trends in haematological profile

Parameters	Days on hospitalization							
	1	5	8	15	24	35	42	49
HB (g/dl)	4.2	3.7	3	3.6	4.0	6.6	8	9.1
Hct (%)	12.9	11	9	11	13	19.7	24.2	28.5
RBC Count ($\times10^9$/L)	1.36	1.15	0.97	1.17	1.30	1.84	2.3	2.78
Total WBC ($\times10^9$/L)	2.41	1.0	1.0	1.4	1.2	1.26	1.47	1.540
Neut. $\times10^9$/L /(%)[a]	1.28 (52)	0.35 (35)	0.26 (26)	0.49 (35)	0.18 (15)	0.3 (23.8)	0.26 (17.7)	0.35 (22.7)
Lymph $\times10^9$/L /(%)[a]	0.63(25)	0.48 (48)	0.64 (64)	0.66 (47)	0.95 (79)	0.88 (70)	1.12 (76.4)	1.10 (71.2)
Mono $\times10^9$/L (%)[a]	0.50 (21)	0.13 (13)	0.08 (8)	0.2 (14)	0.05 (4)	0.06 (4.5)	0.05 (3.2)	0.07 (4.3)
Eos/ $\times10^9$/L (%)[a]	0.00 (0.1)	0.04 (4)	0.02	0.06	0.03	0.01	0.025	0.02

Parameters	Days on hospitalization							
	1	5	8	15	24	35	42	49
Baso $\times 10^9$/L (%)[a]	0.00 (0.2)	0	(2) 0	(4) 0	(2) 0	(0.8) 0.011 (0.9)	(1.7) 0.01 (1.0)	(1.3) 0.008 (0.5)
Platelets ($\times 10^9$/L)[a]	112	95	78	89	166	145	139	138

Key: *HB=haemoglobin concentration, Hct= haematocrit, RBC= red blood cell, WBC= white blood cell count, Neut= Neutrophil count, Lymph = lymphocyte count, Eos=eosinophil count, Baso= basophil count,* [a] *=Absolute cell count are displayed with relative cell count enclosed in parenthesis*

Table 2. Detailed bone marrow findings

Parameters	Findings/ Comments
Fragments	Marked hypocellular marrow fragment and trail
Myeloid: erythroid (M: E) ratio	1:1
Erythroid activity	Reduced
Erythropoiesis	Micro-normoblastic,erythroid clusters, moderate megaloblastic changes seen.
Myelopoiesis	Markedly reduced with maturation arrest. There is preponderance of large blast cells having deeply basophilic granular cytoplasm with Auer rods, round nuclear outline, and open nuclear chromatin pattern with some harboring one or two nucleoli. These cells constitute more than 20% of the marrow nucleated elements.
Megakaryopoiesis	Megakaryocytes were present with few hypo-lobulated forms seen.
Lymphopoiesis	There is infiltration of the marrow by small to medium sized mononuclear cells.
Plasma cells	Present but not increased
Other cells	Occasional naked cells seen
Conclusion/Diagnosis	Bone marrow failure: Acute myeloblastic leukaemia (FAB M2), Myelophthisic anaemia.

Key: *French-American-British FAB- M2 classification of acute myeloblastic leukaemia = Acute myeloblastic leukemia with maturation*

3. DISCUSSION

3.1 Medical, Ethical and Resource Challenge

Management of Jehovah's Witnesses patients presenting with severe anaemia poses unusual medical and ethical challenge [3]. The health care personnel in a bid to conscientiously fulfill his duty of care to save patient's life in line with established medical guidelines feels frustrated when the patient refuses recommended therapy. However, the enthusiasm to provide medical care needs to be guided by the recognition and respect for the rights and personal dignity of patients as individuals [4,5]. Additionally, respect for patients' autonomy is recognized as one of the fundamental principles of biomedical ethical behavior which allows patients the right to make decisions about their medical care [4].

This understanding can assist in avoiding needless confrontations and wastage of precious time that could be channeled into exploring effective lifesaving alternative non-blood therapy. The management of these patients was further compounded by the challenging difficulties in accessing the relevant drugs and the associated cost implications especially in poor resource settings of most developing countries.

3.2 Disease Severity

The haematological and bone marrow (BM) features of the index patient fulfill the criteria for classification as severe aplastic anaemia based on the class definition developed by Camitta et al and validated by Bacigalupo et al. (BM cellularity < 25% or 25-50% with <30% residual haemopoietic cell, Reticulocyte count < 20 $\times 10^9$/L, neutrophils < 0.2 $\times 10^9$/L.) [6,7].

A number of guidelines suggest the transfusions of red cell when the haemogram drops below the threshold of 7g/dL in patients with aplastic anaemia to maintain a safe blood count [8,9,10]. It is recommended to give prophylactic platelet transfusions when the platelet count is < 10 ×10

^{9}/L or < 20 ×10 ^{9}/L in the presence of fever [11]. However, there are concerns that allogenic blood transfusion in these patients results in increased platelet refractoriness, as well as an increased risk of graft rejection after allogeneic bone marrow transplant [12].

3.3 Multi-modality Therapy

In the management of the severe aplastic pancytopenia in our patient, transfusion of allogenic blood components was not an option for religious reasons. Therefore, a multi-modal blood transfusion alternative approach was used to improve oxygen delivery and haematopoiesis.

3.4 Recombinant Human Erythropoietin (RHuEPO) Therapy

Erythropoietin (EPO) is essentially for the proliferation, differentiation, and maturation of red blood cells [13,14,15]. Recent studies have suggested that erythropoietin has immuno-modulatory, anti-inflammatory, anti-tumour, and neuroprotective properties [14,15].

From its initial approval in 1988 for correction of anaemia of chronic renal failure, the introduction of recombinant human erythropoietin (RHuEPO) has significantly changed the treatment of moderate to severe anaemia of various aetiology [16,17,18].

There are currently four different RHuEPOs: alpha, beta, delta, and omega. However, only EPO-alpha and EPO-beta are currently available for clinical use.

Anaemia of chronic illness as seen in most causes of aplastic anaemia is associated with blunted response to endogenous erythropoietin. However, high pharmacologic dose of erythropoietin can overcome the erythropoietin resistance [19,20]. Several treatment protocols have documented impressive results with RHuEPO daily doses as high as 40,000 international units (I.U) without any significant adverse events [10,21]. Considering the cost implications, we commenced our patient on a moderate dose of 12,000 I.U per day and monitored response for possible dosage adjustment as necessary. The dose of EPO used was however, significantly high when compared with our hospital EPO protocol of 4,000 I.U given subcutaneously 2-3 times weekly.

Our experience collaborates previous observations that the optimization of erythropoietin therapy is critical in rapid expansion of haematocrit level and improved clinical outcome in patients with severe anaemia [10,21,22].

3.5 Use of Artificial Oxygen Carrier

In recent times, there is a growing interest in scientific research and development of artificial oxygen carriers and other blood transfusion alternative therapies [23,24]. The key driver in these research efforts is the desire to design universal oxygen carrying solutions that can replace the oxygen storage, transport and delivery functions of red blood cells which will greatly improve clinical outcomes both for trauma victims and patients undergoing high-blood-loss surgical procedures as well as address the concerns of Jehovah's Witnesses and others who have religious objections to receiving transfused blood. Artificial oxygen carriers can be grouped into hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbon-based oxygen carriers (PFCs) [24]. In recent years, focus on the potential clinical use of artificial oxygen carriers has been on HBOCs. Clinical trials have consistently demonstrated that survival of patients with severe anaemia for whom red blood cell transfusion was not an option was clearly and significantly higher if treated with an HBOC [25,26].

Consequently, synthetic haemoglobin-based oxygen carriers has been recommended for Jehovah's Witness patients with severe life-threatening anemia (Hb level less than 5 or 5 to 7 g/dL with associated symptoms of hypoperfusion) [21,26].

Currently, Hemopure (HBOC-201), which is a purified, cross-linked acellular bovine Hb in a modified lactated Ringer's solution is the only HBOC available for clinical use [27,28]. One unit of Hemopure includes 32.5 g of polymerized bovine Hb in approximately 225 to 250mL of a solution similar to lactated Ringer's, increases the plasma Hb level by 0.63 g/dL, and has a half-life of approximately 19 hours [27].

The use of the drug requires patient consent, institutional review board approval, and Food and Drug Administration (FDA) emergency investigational new drug (IND) approval for use in individual patients [21].

In situations of life-threatening critical anaemia, as seen in the index patient, HBOCs can bridge

patients until endogenous Hb levels improves in response to pharmacologic treatment strategies. In our patient, improvements in haematological parameters became clinically evident by the third week of supportive treatment.

During this period, concerted efforts were made to secure a compassionate regulatory approval for the emergency use of the synthetic polymerized bovine Hb Oxygen Carrier (Haemopure) in our patient. However, the drug could not be procured from the manufacturers in South Africa as it was temporarily out of supply at the moment of need.

3.6 Replenishing Iron and Vitaminin Stores and Other Supportive Care

Effective erythropoiesis requires the availability of adequate store of iron as well as vitamin B12, vitamin C, and folate. However, functional iron deficiency which is common in anaemia due to chronic illnesses can compromise the management of these patients. The use of intravenous iron infusion in the form of iron dextran or iron sucrose at doses based on the calculated iron deficit is recommended. One major concern is an immediate anaphylactic-type hypersensitivity reaction which can occur in some individuals. Hence, the need for a test dose prior to the administration of first therapeutic dose. Recently, oral iron preparations in ampoule forms such as Totherma® have been developed with capability of rapidly building iron stores [29].

Prophylactic antibiotic and antifungal drugs are recommended in patients with neutrophil count less than 0.5 x 10^9/L or earlier in febrile neutropenia patiensts [1].

3.7 Granulocyte Colony-stimulating Factor (G-CSF)

Granulocyte colony-stimulating factor (G-CSF), also known as colony-stimulating factor 3 (CSF-3), is an endogenous glycoprotein that stimulates the production, differentiation, maturation and release of granulocytes from the bone marrow [30,31].

Filgrastim(non-glycosylated rHuG-CSF) and Lenograstim (glycosylated rHuG-CSF)) are analogs of naturally occurring G-CSF synthesized by recombinant DNA (rDNA) technology [32,33]. Pegfilgrastim is a pegylated form of non-glycosylated HuG-CSF which is obtained by the attachment of polyethylene glycol (PEG) moiety. This modification reduces renal excretion and masks the proteolytic cleavage sites, resulting in elevated G-CSF serum levels for up to 14 days after a single injection [33].

Our patient received 300mg of Filgratim subcutaneously daily for four weeks with significant improvement in absolute white blood cell count. Treatment with G-CSF is critical in sepsis prevention and control by enhancing leucocyte count and activation of neutrophil, monocyte and macrophage.

3.8 Thrombopoietin Stimulating Agents

Two thrombopoietin (TPO) receptor agonists (eltrombopag and romiplostim) have been approved for the treatment of aplastic anemia. Thesedrug, although bear no structural resemblance to thrombopoietin bind and activate the TPO receptor. Romiplostim is a recombinant protein composed of a biologically active peptide and a fragment crystallizable (Fc) domain of immunoglobulin G (peptibody), while Eltrombopag is an orally available, small organic compound. Results of phase I-II trials demonstrated that romiplostim given as a weekly subcutaneous injection for 1-6 weeks results in doubling of platelet counts in most treated patients with minimal adverse effects [34,35]. In a randomized, double-blind, placebo-controlled phase III trial on idiopathic thromdocytopaenic(ITP) patients given daily oral treatment with either placebo or eltrombopag 50 mg, platelet responses were observed in 59% of eltrombopag-treated patients and in 16% of patients in the placebo arm without significant adverse events [36].

Our patient had an impressive response with a two-week course of oral Eltrombopag 50mg daily.

3.9 The Lessons

Treatment of acute leukaemia in our patient with intensive chemotherapy without red cell and platelet support presented a serious dilemma because of the slime prospect of the patient making it through the nadir of myelo-suppression without transfusion support [37]. In this scenario, the use of less myelo-suppressive regime for palliative care has been advocated [38,39]. Considering the severity of anaemia in our patient at presentation we were reluctant to give

high intensive chemotherapy. We adopted a 'palliative' approach by administering intravenous Vincristine 1.4mg/m^2 weekly.

The immediate and urgent priority in our management of the patient was to provide alternative non-blood haematological supportive care in preparation for referral for definitive bone marrow transplant procedure abroad as the facility was not yet available in the country.

Bone marrow stem cell transplant is considered the standard of care for treatment of severe aplastic anaemia [40,41,42]. The procedure usually involves pre-treatment with high doses of chemotherapy with or without total body irradiation therapy to destroy malignant cells followed by stem cells replacement.

An expected complication of the pre-transplant conditioning chemotherapy is severe pancytopaenia, which often necessitates the transfusion of blood products.

There is an increasing body of evidence demonstrating the feasibility and safety of bone marrow transplant, with appropriate supportive measures without blood transfusion [43,44,45,46,47]. The success of these programs was due to algorithms that optimize pre-transplant parameters with haematopoiesis stimulating agents and by strict adherence to conservative [48].

There is paucity of data on blood transfusion alternative management of aplastic anaemia in poor resource settings like ours. A number of reports from other areas have documented good outcome using the multi-modality pharmacologic approach [22,49,50]. Jakiel et al, reported successful obstetric and hematologic outcome of aplastic anemia in a pregnant Jehovah's Witness without the use of blood [22]. These measures have proven to be effective adjuncts in transfusion-free stem cell transplant procedures in Jehovah's Witnesses patients with aplastic anaemia [49,50]. This therapeutic approach significantly reduced nadir drops in blood cell parameters during phases of severe myelo-supression in the course of treatment as well as served as a bridge to hematopoietic stem cell transplantation in refractory aplastic anaemia [48,49,50].

Our experience in the management of this patient offers some key lessons. Firstly, it highlights the positive impact of physician's reassuring attitude and perseverance on treatment out-come in life threatening critical care situations even when the prognosis seems to be uncertain or hopeless.

Secondly, Prompt institution of multi-modality alternative therapy with optimal doses of haematopoiesis stimulating agents can be life-saving in severe anaemia patients who refuse blood transfusion.

Thirdly, the difficulties encountered in procuring the relevant drugs for this treatment modality can be reduced by including the drugs in the hospital and national essential drug list. This will go a long way in facilitating access to the drugs as well as reducing their costs.

Finally, it is important to recognize the impact of social support in the care of patients with chronic and life-threatening illness, especially where efficient health insurance scheme is lacking. Social support groups can help to ease the burden on the patient and care-givers who are usually under severe physical, financial and psychosocial stress. The authors sincerely acknowledge the huge support and assistance the local Jehovah's Witnesses community offered the patient as well as their roles in the procurement of drugs used in the patient's management.

4. CONCLUSION

Optimized combination therapy of haematopoiesis stimulating agents results in significant rise blood counts indices and improved out-come in a Jehovah's witness patient with severe aplastic anaemia.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Marsh JCW, Ball SE, Jamie Cavenagh J, et al. Guidelines for the diagnosis and management of aplastic anaemia. British Journal of Haematology. 2009;147:43–70
2. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. Blood. 2006;108:2509–2519.
3. Bodnaruk ZM, Wong CJ, Thomas MJ. Meeting the clinical challenge of care for Jehovah's Witnesses. Transfus Med Rev 2004;18:105-116
4. Muramoto O. Bioethics of the refusal of blood by Jehovah's Witnesses: part 1. Should bioethical deliberation consider dissidents' views? J Med Ethics. 1998;24:223-230.
5. Ridley DT. Jehovah's Witnesses' refusal of blood: obedience to scripture and religious conscience. J Med Ethics 1999;25:469-472.
6. Camitta, BM, Rappeport JM, Parkman R, Nathan DG. Selection of patients for bone marrow transplantation in severe aplastic anemia. Blood. 1975; 45: 355–363.
7. Bacigalupo A, Hows JM, Gluckman E, Nissen C, Marsh J, Van Lint MT, Congiu M, De Planque MM, Ernst P, McCann S. Bone marrow transplantation (BMT) versus immunosuppression for the treatment of severe aplastic anaemia (SAA): a report of the EBMT SAA Working Party. British Journal of Haematology. 1988;70(2):177-182
8. Beliaev AM, Marshall RJ, Smith W, et al. Mortality risk stratification in severely anaemic Jehovah's Witness patients. Intern Med J. 2012;42:e1-3.
9. Beliaev AM, Marshall RJ, Smith W, et al. Treatment monitoring and mortality risk adjustment in anaemic Jehovah's Witnesses. ANZ J Surg. 2013;83:161-4
10. Hughes DB, Ullery BW, Barie PS. The contemporary approach to the care of Jehovah's Witnesses. J Trauma. 2008;65:237-247
11. Kelsey P, Murphy M.F, Brown M, Carrington P, Hall G, Jeffrey RR, Machin S, Taylor C, Thomas D. Guidelines for the use of platelet transfusions. British Journal of Haematology 2003;122:10–23.
12. Kaminsky ER, Hows JM, Goldman JM, Batchelor JR. Pretransfused patients with severe aplastic anaemia exhibit high numbers of cytotoxic T lymphocyte precursors probable directed at non-HLA antigens. British Journal of Haematology. 1990;76:401–405.
13. Silva M, Grillot D, Benito A, et al. Erythropoietin can promote erythroidprogenitor survival by repressing apoptosis through Bcl-XL and Bcl-2. Blood. 1996;88:1576–1582.
14. Huraib S, Abu-Aisha H, al-Momen A, et al. Effect of recombinanthuman erythropoietin on lymphocyte phenotyping and phagocyte activityin hemodialysis patients.Am J Kidney Dis. 1997;29:866–870.
15. Tilbrook PA, Klinken SP. The erythropoietin receptor. Int J Biochem Cell Biol. 1999;31:1001–1005.
16. Winearls CG, Oliver DO, Pippard MJ, et al. Effects of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet.1986;ii:1175–1178.
17. Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anaemiaof end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and II clinical trial. N Engl J Med. 1987; 316:73–78.
18. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant humanerythropoietin in anemic patient with end-stage renal disease. Results of a phase III multicenter clinical trial. Ann Intern Med. 1989; 111:992–1000.
19. Elliott J, Mishler D, Agarwal R. Hyporesponsiveness to erythropoietin: causes and management. Adv Chronic Kidney Dis. 2009;16:94-100.
20. Charles A, Purtill M, Napolitano LM. Recombinant human erythropoietin in severe anaemia: Issues of dosing and duration. Anaesth Intensive Care. 2006; 34:793-6
21. Posluszny JA (Jr), Napolitano LM. How do we treat life-threatening anemia in a Jehovah's Witness patient?. Transfusion. 2014;54:3026-3034.

22. Jakiel G, Ciebiera M, Słabuszewska-Jóźwiak A, Horosz B, Bińkowska M, Wilińska M, Malec-Milewska W. Successful obstetric and hematologic outcome of aplastic anemia in a pregnant Jehovah's Witness. Int J Immunopathol Pharmacol. 2016;29(3):543–548.
23. Henkel-Honke T, Oleck M. Artificial oxygen carriers: A current review. AANA Journal. 2007;75(3):205–211.
24. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. Curr Pharm Des. 2005; 11(31):4099–4114.
25. Weiskopf RB, Beliaev AM, Shander A, Guinn NR, Cap AP, Ness PM, Silverman TA. Addressing the unmet need of life-threatening anemia with hemoglobin-based oxygen carriers. Transfusion. 2017;57(1): 207–214.
26. Lundy JB, Lewis CJ, Cancio LC, et al. Experience with the use of Hemopure in the care of a massively burned adult. Int J Burns Trauma. 2014;4:45-48.
27. Jahr JS, Mackenzie C, Pearce LB, et al. HBOC-201 as an alternative to blood transfusion: efficacy and safety evaluation in a multicenter phase III trial in elective orthopedic surgery. J Trauma. 2008;64: 1484-1497
28. Donahue LL, Shapira I, Shander A, et al. Management of acute anemia in a Jehovah's Witness patient with acute lymphoblastic leukemia with polymerized bovine hemoglobin-based oxygen carrier: A case report and review of literature. Transfusion. 2010;50:1561-1567.
29. ClinicalTrials.gov identifier (NCT number): NCT04309669. Assessment of the eFficacy, the Onset-of-Action and the Safety of Tot'héma® in Adults with Moderate Iron Deficiency Anaemia (FAST). U.S. National Library of Medicine; 2021.
30. Deotare U, Al-Dawsari G, Couban S, Lipton JH. G-CSF-primed bone marrow as a source of stem cells for allografting: Revisiting the concept". Bone Marrow Transplantation. 2015;50(9):1150–1156.
31. Tay J, Levesque JP, Winkler IG (December 2016). "Cellular players of hematopoietic stem cell mobilization in the bone marrow niche". International Journal of Hematology. 2016;105(2):129–140.
32. Ria R, Reale A, Melaccio A, Racanelli V, Dammacco F, Vacca A. Filgrastim, lenograstim and pegfilgrastim in the mobilization of peripheral blood progenitor cells in patients with lymphoproliferative malignancies. Clin Exp Med. 2015;15(2): 145–150.
33. Kubota N, Orita T, Hattori K, et al. Structural characterization of natural and recombinant human granulocyte colony-stimulating factors. J Biochem. 1990;107: 486–492.
34. Wang B, Nichol JL, Sullivan JT. Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand. Clin Pharmacol Ther. 2004;76(6):628–638
35. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008;371:395–403
36. Jenkins JM, Williams D, Deng Y, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. Blood. 2007;109(11):4739–4741
37. Ferrara F, Barosi G, Venditti A, Angelucci E, Gobbi M, Pane F, Tosi P, Zinzani P, Tura S. 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;27:997–999
38. Chang Y, Guyatt GH, Teich T, Dawdy JL, Shahid S, Altman JK, et al. Intensive versus less-intensive antileukemic therapy in older adults with acute myeloid leukemia: A systematic review. PLoS ONE. 2021;16(3):e0249087.
39. Griffiths EA, Carraway HE, Chandhok NS, Prebet T. Advances in non-intensive chemotherapy treatment options for adults diagnosed with acute myeloid leukemia. Leukaemia Research. 2020;91:106339.
40. Fattizzo, B., Giannotta, JA, Barcellini W. Mesenchymal Stem Cells in Aplastic Anemia and Myelodysplastic Syndromes: The "Seed and Soil" Crosstalk. International journal of molecular sciences. 2020;21(15): 5438-5446.
41. Andrea B, Sabrina G. Stem cell transplantation in aplastic anemia: Impact on choices for first line therapy. HemaSphere. 2019;3(S2):15-17.
42. Shroff G, Gupta R, Zadeng L. Human embryonic stem cell therapy for aplastic anemia. Clinical case reports. 2017;5(6): 919–922.
43. Beck A, Lin R, Reza Rejali A. et al. Safety of bloodless autologous stem cell

transplantation in Jehovah's Witness patients. Bone Marrow Transplant. 2020;55:1059–1067.
44. Joseph NS, Kaufman JL, Boise LH, Valla K, Almaula DK, Obidike CO, et al. Safety and survival outcomes for bloodless transplantation in patients with myeloma. Cancer. 2019;125:185–193.
45. Khan R, Mott SL, Schultz A, Jethava YS, Tricot G. Bloodless tandem autologous transplant in Jehovah's Witness patients. Bone Marrow Transpl. 2018;53:1428–1433.
46. Ford PA, Grant SJ, Mick R, Keck G. Autologous stem-cell transplantation without hematopoietic support for the treatment of hematologic malignancies in Jehovah's Witnesses. J Clin Oncol. 2015;33:1674–1679.
47. Ballen KK, Becker PS, Yeap BY, Matthews B, Henry DH, Ford PA. Autologous stem-cell transplantation can be performed safely without the use of blood-product support. J Clin Oncol. 2004;22: 4087–4094.
48. Coltoff A, Aditya S, Solmaz A, Steinberg A. Single-institution experience of performing bloodless transplant in Jehovah's Witness patients. Hematol Oncol Stem Cell Ther. 2019;12:44–49.
49. Mazza P, Palazzo G, Minoia C, Amurri B, Pisapia G. Autologous and allogeneic stem cell transplant in Jehovah's Witnesses: a single-center experience on 22 patients. Bone Marrow Transplantation. 2016;51:1002–1003
50. Mazza P, Prudenzano A, Amurri B, Palazzo G, Pisapia G, Stani L et al. Myeloablative therapy and bone marrow transplantation in Jehovah Witnesses: single centre experience. Bone Marrow Transplant 2003;32:433–436.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/70444