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CASE REPORT

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Management of thymoma-associated pure red cell aplasia: A novel use of blood substitute HBOC-201 in a Jehovah's Witness

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Abstract

Pure red cell aplasia (PRCA) is a rare paraneoplastic syndrome occasionally associated with thymomas. Here, we report on the first ever use of a bovine hemoglobin-based oxygen carrier, HBOC-201 (HbO2 Therapeutics LLC; Hemopure®, Waltham, MA) for the supportive management of pure red cell aplasia in a Jehovah Witness patient.

KEYWORDS

hemoglobin-based oxygen carrier, hemopure, pure red cell aplasia, red blood cell alternatives

1 | INTRODUCTION

Pure red cell aplasia (PRCA) is a disorder characterized by: normocytic normochromic anemia with preserved white cell and platelet counts, severe reticulocytopenia and absence or profound reduction in erythroid precursors in the bone marrow. There is a strong historical association between pure red cell aplasia PRCA and thymoma.[1] Thymoma-associated PRCA (taPRCA) is believed to be part of a paraneoplastic phenomenon in which autoantibodies cause disruption of erythroid differentiation. Surgical resection of a thymoma can treat taPRCA, but interestingly, a subset of patients develop taPRCA after thymectomy.[1] Primary treatment is immunosuppressive therapy with steroids and cyclosporine A (CSA).[2] Unfortunately, recovery of erythrocytes and erythroid precursors can take many months and patients are managed with supportive blood transfusions. However, patients who decline blood products require an alternative method of hemoglobin support.

Here, we report on the first ever use of a bovine hemoglobin-based oxygen carrier, HBOC-201 (HbO2 Therapeutics LLC; Hemopure®, Waltham, MA) for the supportive management of a resected Stage IVA Type B2 Thymoma-associated pure red cell aplasia in a 57-year-old Jehovah Witness. The patient received more than 20 units of HBOC-201 and was showing early signs of red blood cell count recovery. Although the patient did not survive, administration of the HBOC-201 did sustain her long enough to allow for administration of immunosuppressive therapy which ultimately improved erythropoiesis. Thus, administration of alternative hemoglobin-based oxygen carriers in the setting of red cell aplasia associated with thymomas warrants further investigation.

2 | CASE REPORT

Here, we present a 57-year-old Jehovah Witness (JW) woman, presented to Memorial Sloan Kettering (New York, NY) reporting several weeks history of headaches, dyspnea on exertion and fatigue. She was found to have a hemoglobin of 4.1 g/dL. She had a history of thymoma which was recently treated with neoadjuvant cisplatin, cyclophosphamide, and doxorubicin followed by surgical resection. Given the severity of her anemia, history of a thymoma, and lack of a reticulocyte response without evidence of bleeding and/or hemolysis, the diagnosis of taPRCA was inferred. We began empiric treatment for PRCA with prednisone 1 mg/kg as first-line therapy.[2] We stimulated her endogenous erythropoiesis with intravenous iron, vitamin B12, folic acid, subcutaneous erythropoietin and we began to investigate blood product alternatives.[3] We submitted a single patient use (SPU) investigational new drug application (IND) to the US Food and Drug Administration (FDA) for a hemoglobin alternative, HBOC-201 (Hemopure, HbO2 Therapeutics®, Waltham, MA) with emergency institutional review (IRB) and the patient's informed consent.

On hospital day two, we added CSA and adjusted the dose based on daily CSA levels. Her hemoglobin dropped to 2.9 g/dL, and she was transferred to the intensive care unit. On hospital day 4, the patient received an initial loading dose of three units of HBOC-201 and the patient's vital signs and encephalopathy markedly improved. After the initial loading dose of HBOC-201, she was maintained subsequently on two units daily of HBOC-201. Her detailed transfusion history and laboratory findings are outlined in Table 1. Given the properties of HBOC-201, a polymerized bovine hemoglobin solution carried in the plasma phase, monitoring hemoglobin, and hematocrit levels, based on absorption spectra, was difficult.[4,5] We worked closely with laboratory medicine and blood bank physicians to ensure appropriate monitoring. The patient was monitored clinically for symptoms and laboratory markers of tissue ischemia and her methemoglobin (MetHb) levels.

After administration of HBOC-201, the patient developed asymptomatic methemoglobinemia. She was treated with ascorbic acid, followed by IV methylene blue. The patient experienced headaches, abdominal cramps, and progressive dysphagia to both solid and liquids. On infusion day five, she was found to have left lower lobe pneumonia. Additionally, she was found to have Klebsiella and Enterococcus species growing in her urine and started on piperacillin/tazobactam. On infusion day ten, she developed worsening nausea, vomiting, and abdominal pain. There was no radiographic evidence of obstruction. She became increasingly somnolent. Her laboratories on infusion day ten were notable for a recovering absolute reticulocyte count of 102.3 K/mcL; however, she was more hypoxic. She developed atrial fibrillation with rapid ventricular rate and acute hypotension. Her echocardiogram showed an underfilled left ventricle with preserved ejection fraction. Her right ventricle was enlarged and hypokinetic. She was urgently intubated and started on phenylephrine for hypotension. Shortly after intubation, on infusion day 11, the patient died from tissue ischemia leading to cardiopulmonary arrest.

3 | DISCUSSION

Even though the patient died from the consequences of her prolonged anemia, there is clinical rationale for using HBOC-201. Furthermore, HBOC-201 supported her temporarily to allow some reticulocyte recovery from PRCA. HBOC-201 was chosen because it has a hemoglobin concentration of 13 g/dL and 50% saturated (P50) of 40 mm Hg (human hemoglobin P50 is 27 mm Hg).[6] The iso-oncotic properties of HBOC-201 allow for volume expansion while providing a source of oxygen-carrying hemoglobin. Therefore, HBOC-201 can more effectively increase total hemoglobin concentration and offload oxygen more efficiently to ischemic tissues. Clinically, HBOC 201 has been studied in multiple phase I, phase II, and phase III clinical trials in cardiac surgery, noncardiac surgery, and orthopedic surgeries.[4] Some well-published side effects of HBOC-201 treatment are related to vasoconstriction due to NO scavenging that can increase both systemic and pulmonary blood pressures. Our patient did not experience hypertension but received low-dose furosemide for her left-sided pleural effusion after receiving 16 units of HBOC-201. After 20 units of HBOC-201, she had normal pulmonary artery pressures. Other NO side effects experienced included abdominal pain, nausea, and dysphagia, all of which are suspected to be due to the interaction between NO and smooth muscle dysfunction.

HBOC-201 is also associated with an increase in metHb. HBOC-201 has absent MetHb-reductase, an enzyme contained in red blood cells responsible for reducing metHb (Fe3+) to Hb (Fe2+). Mild elevations of metHb are typically asymptomatic, but levels >20% may adversely impact oxygen delivery. Normally, MetHb shifts the oxyhemoglobin curve to the left (higher O_2 affinity). In our patient, the high proportion of total hemoglobin having lower oxygen affinity may have helped compensate for any >left-shift effect of the metHb. We administered ascorbic acid and methylene blue, but despite this, the elevated metHb level and the low total hemoglobin concentration resulted in persistently low levels of functional hemoglobin and eventually in organ-specific hypoxia.

After six days of immunosuppression, our patient showed early signs of reticulocyte recovery. Furthermore, the patient's arterial lactate level remained stable for the first eight days of HBOC-201 infusions indicating

TABLE 1 During HBOC-201 treatment

Date	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
WBC (4.0-11.0 K/mcL)	7.3	7.8	9.0	10.10	9.50	13.00	16.20	18.20	23.70	31.70	25.70	27.20
RBC (3.80-5.00 M/mcL)	0.8	0.8	0.6	0.45	0.47	0.69	0.41	0.41	0.42	0.47	0.53	0.48
Hemoglobin (11.2-15.4 g/dL)	2.9	3.0	3.7	4.00	4.10	5.00	4.50	4.7	4.80	4.30	5.10	5.30
Hematocrit (34.3%-46.0%)	7.7	7.6	5.5	4.40	4.40	6.30	3.90	4.10	4.70	4.90	6.90	5.90
Platelets (160-400 K/mCL)	296	295	246	228	240	220	233	220	194	151	157	136
Absolute Retic (36.4-111.1 K/mcL)	–	–	–	–	4.00	10.40	–	–	–	–	102.30	–
Lactic Acid, Arterial, unless otherwise noted (0.3-1.3 mM/L)	0.8 (venous)	–	0.8	0.60	–	1.10	1.30	–	1.50	2.10	4.90 (venous)	–
Steroids (1mg/kg)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MetHb Arterial unless otherwise noted (0.0%-1.5%)	–	18.4	18.4	24.1	23.2	17.9	25	26 (venous)	21.3	21.3	20.3 (venous)	17.6 (venous)
Cyclosporine A Level (ng/mL)	35.70	-	113.00	–	102.40	118.70	–	74.00	–	–	208.70	496.70
HBOC-201 (# Units)	–	3.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	–

adequate tissue oxygenation during that phase of treatment. HBOC-201 allowed for temporary support to allow for erythropoiesis.

Unfortunately, she had eventual cardiopulmonary arrest because of her prolonged and life-threatening anemia. To our knowledge, this is the first use of HBOC-201 in a patient with taPRCA.

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CONFLICT OF INTEREST

JVM reports research funding from Janssen Pharmaceuticals. GJR reports grant and nonfinancial support from Novartis, Pfizer, Roche and Takeda. GPD is employed by Hemoglobin Oxygen Therapeutics, LLC. MMR, CG, and STA have nothing to disclose.

AUTHOR CONTRIBUTIONS

MMR and JVM: were the benign hematologists who diagnosed the pure red cell aplasia and made the decision to treat with a blood substitute. GJR: is the medical oncologist who treated her thymoma. CG and STA: were the blood bank and laboratory medicine physicians, respectively, who advised on which blood substitute to choose and how to monitor her laboratory parameters during treatment. GPD: contributed by reviewing and helping to edit this manuscript.

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