Case Report

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Dimethyl Sulfoxide-Induced Toxicity in Cord Blood Stem Cell Transplantation: Report of Three Cases and Review of the Literature

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Key Words
Cord blood cells · Dimethyl sulfoxide · Umbilical cord blood transplantation

Abstract
Umbilical cord blood transplantation using nonmyeloablative conditioning is currently considered by many as a valid potential alternative for any patient who requires an unrelated donor allograft and who is without a suitably matched and readily available volunteer. Dimethyl sulfoxide (DMSO) has been used for years as a cryoprotectant agent; it acts by penetrating the cell and binding water molecules and it has been described as harmless for the individual who receives it in limited amounts. In this paper, we describe 3 cases of DMSO-induced toxicities and briefly review the most common adverse reactions of the DMSO when used as a cryopreservation agent for the long-term storage of cord blood cells. Two of the 3 cases had a dismal prognosis. A brief review of the literature is presented.

Introduction

Cord blood cells (CBC) from both related and unrelated donors are being used as a source of hematopoietic stem cells (HSC) in a variety of hematological disorders. The advantages of CBC are the immediate availability, the absence of risks to the donor, the potentially reduced risk of GVHD and a lower need for HLA compatibility between the donor and the recipient [1].

Dimethyl sulfoxide (DMSO) has been commonly used for several years as a cryoprotectant agent; it acts by penetrating the cell and binding water molecules. By doing so, it blocks the efflux of water and prevents cellular dehydration, maintaining stable pH, intracellular salt concentration, and preventing the formation of the ice crystals which endanger cell integrity. Cryopreservation allows for the long-term storage of CBC. DMSO is the most frequently used cryopreservation agent [2]. However, its use has been reported to induce complications ranging from nausea, vomiting, abdominal pain to life-threatening cardiac arrhythmias or cardiopulmonary events, after infusion of cryopreserved bone marrow, cord blood or peripheral HSC.

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Case Reports

Case 1

A 33-year-old male, O+ blood type, with BCR/ABL(+) chronic myelogenous leukemia was treated with hydroxyurea for 1 year and later on with imatinib mesylate for 3 years. An HSC transplant was done using a reduced-intensity conditioning regimen [3], employing cells from an O+ Caucasian male umbilical cord unit that was a 4/6 match. The mismatches were in class I. He received 4.5×10^7/kg of total nucleated cells and 1.7×10^5 of CD34+ cells. The unit was thawed and then infused without washing the DMSO, the patient receiving a total volume of 174 ml of the product. During the infusion the patient developed bradycardia, abdominal pain and nausea; an antihistamine and an antiemetic were given. Twenty-four hours later he developed anasarca and hypertension coupled with a gradual rise in the creatinine levels which reached 8.4 mg/dl on day +4, returning to normal levels on day +19 after being treated only with diuretics. The placental cells failed to engraft, and the patient remains in remission while being treated with imatinib mesylate.

Case 2

A 21-year-old female, blood type B+, with acute myelogenous leukemia in a first remission was allografted using a reduced intensity conditioning regimen [3] and HSC from two unrelated umbilical cord cells with a 6/6 HLA compatibility: one unit was from a female O+ Chinese; it had 1.25×10^6 CD34+ cells; the other unit was from a male Caucasian A+; it had 2.85×10^6 CD34+ cells. The cells of the two cords were infused immediately after thawing, without washing the DMSO. One hour later the patient developed a headache, cutaneous rash, hypotension, bradycardia and finally shock; she was admitted to the intensive care unit where she was given aggressive hydration, intravenous steroids and inotropics; an endotracheal tube was inserted. An acute hemolysis episode was evident because discolored urine was passed and free haptoglobin and hemogobin levels dropped abruptly. The antiglobulin test was persistently negative. The creatinine levels rose to a maximum of 6.1 mg/dl on day +6 and the patient was started on hemodialysis every 48 h; she developed neutropenic fever 8 days after the transplant. She engrafted and became a mixed chimera (27% donor cells) on day +21. The patient died as a result of nosocomial bloodstream infection by *Pseudomonas aeruginosa* on day +21.

Case 3

This 10-year-old female, O+ blood type, with Fanconi anemia was treated initially with prednisone, folic acid and red blood cell transfusions. She was given an allograft using a reduced intensity conditioning regimen and employing HSC from two unrelated cord blood units with 5/6 and 4/6 compatibilities, respectively. Both units stemmed from Mexican donors A+, one of them containing 1.47×10^5 CD34+ cells and the other one containing 1.12×10^5 CD 34+ cells, making a total of 2.59×10^5 CD34+ cells. The units were infused without washing the DMSO and 8 h later she was admitted to the intensive care unit because of progressive hypotension, bradycardia, atrioventricular heart block and severe metabolic acidosis in the presence of normal levels of urea and creatinine. An endotracheal tube was inserted and ventilatory assistance was started but the patient failed to respond and developed cardiac arrest during the irreversible cardiogenic shock.

Table 1. Salient features of the 3 cases of DMSO-associated toxicities

No.	Age years	Sex	Number of cords	Total CD34	Complications	Outcome
1	33	M	1	1.7×10^5	acute renal failure	alive
2	21	F	2	4.1×10^6	acute renal failure, anaphylaxis, hemolysis	sepsis-related death
3	10	F	2	2.6×10^5	arrhythmia	death

Discussion

DMSO [$(CH_3)_2SO$] is an amphipathic molecule with a highly polar domain and two apolar groups, making it soluble in both aqueous and organic media. Due to these physicochemical properties, DMSO is a very efficient solvent for water-insoluble compounds and is a hydrogen-bound disrupter [4]. Despite having been known since the 19th century, mainly due to its use in the wood industry, its biological properties were only discovered in the 1960s. Since then it has been used for diverse laboratory and clinical purposes. DMSO is frequently used as a solvent in biological studies and as a vehicle for drug therapy. DMSO has been used in several therapeutic situations in patients. In 1978 it received approval by the United States Food and Drug Administration for use in the treatment of interstitial cystitis by intravesical instillation [5]. Its effects do not seem to be related to a detectable histamine release from mast cells [6]. It has been used successfully in the treatment of dermatological [7–9], urinary [10], pulmonary [11], rheumatic and renal [12] manifestations of amyloidosis. Basically through its anti-inflammatory and reactive oxygen species scavenger actions, it has been used in several gastrointestinal diseases [13–17]. DMSO crosses the blood-brain barrier [18] and has been effective in the treatment of traumatic brain edema [19]. It has been also used in the treatment of musculoskeletal disorders [20], pulmonary adenocarcinoma [21], rheumatologic diseases [22, 23], chronic prostatitis [24], dermatological diseases [25–27], schizophrenia [28], and as a topical analgesic [29]. In addition, it has been suggested for the treatment of Alzheimer's disease [30]. In the field of HSC transplantation, DMSO is the most frequently used cryopreservation agent.

Several systemic side effects from the use of DMSO have been reported, namely nausea, vomiting [31], diarrhea [32], severe hemolysis mimicking a hemolytic transfusion reaction [33], anaphylactic reactions manifested by rashes, flushing, and bronchospasm [34, 35], renal failure [36], diastolic and systolic hypertension [37], bradycardia, heart block [38–40], and rarely pulmonary edema or cardiac arrest [41, 42]. A significant side effect of DMSO is a garlic-like breath odor and taste in the mouth due to the pulmonary excretion of a small percentage of DMSO as dimethyl sulfide [43]. Its topical application, although well tolerated, can cause mild transient local burning [27], skin rash, and pruritus [25]. A case of sulfhemoglobinemia after dermal application of DMSO in the treatment of interstitial cystitis has been reported, with fatigue, cyanosis, and dyspnea with mild exertion [5].

Cardiovascular side effects, such as sinus bradycardia, transient heart blocks or even fatal cardiopulmonary events, have been reported after infusion of cryopreserved HSC [44]. Nevertheless, the pathogenesis of the aforementioned complications is not clear and is supposed to be multifactorial. Apart from DMSO toxicity, other factors such as cell lysis products, toxicity related to previous treatments or conditioning regimens, hypothermia of the infused cells or acute volume expansion, have been implicated in the pathogenesis of cardiovascular complications following the infusion of cryopreserved HSC. Such complications have usually been observed after administration of HSC when thawing without washing procedure. However, the relevant cardiovascular effects of DMSO remain controversial. Cryopreservation of HSC in 10% DMSO has been the standard procedure in most institutions for both autologous and allogeneic hematopoietic transplants. The grade of DMSO toxicity experienced by patients seems to be related to the amount present in the HSC. Cryopreservation with lower DMSO concentrations would be expected to reduce the toxicity. Consequently, some groups have started using 5% DMSO as cryoprotectant for the autologous PBPC as a standard procedure [45]. Cryopreserving HSC with 5% rather than 10% DMSO could result in improved CD34+ cell viability and possibly a higher potential for in vivo engraftment and ex vivo manipulations of HSC and might be associated with less toxic reactions such as vomiting, cardiac dysfunction, anaphylaxia and acute renal failure [46].

Engraftment after umbilical cord blood transplantation is highly dependent on the nucleated cell and CD34+ cell content. Current standard postthaw processing includes a wash step to remove DMSO, lysed red cells, and stroma. However, some data indicate that the thawing and washing results in a substantial loss of cells, with total nucleated cell loss approaching 20% when compared with prefreeze counts. The wash step has been shown to be responsible for nearly half of the cell loss. Some groups have shown that the elapse of time postwash resulted in further loss of nucleated cells but no detectable significant changes in CD34+ cell content and viability and/or colony-forming units [47]. Some groups have shown that the fast addition of DMSO is essential for improved cryopreservation and postthaw quality assessment results, whereas the speed of DMSO removal after thawing has little influence on the recoveries of CD34+ cells and colony-forming units [48].

The 3 cases which we have presented here have in common that the cells were not washed after thawing. In our two institutions, placental cells are not washed after thawing and, after a total of 65 placental blood allografts, we have seen only these 3 cases of toxicity (3/65 = 4.6%). In case 3, one could argue that for the weight of the patient (28.9 kg), the DMSO contained in the two cords was probably too high; however, this was not the case in patient 2, who also received two cords but had a higher weight (83.2 kg) or patient 1, who received one cord. We suggest that cryopreserving HSC with 5% rather than 10% DMSO could reduce the toxicity, probably with no implications in the engraftment as previously published in the literature. In the 3 cases described here 10% DMSO was used, which probably explains the dismal prognosis in 2 of them. More studies are needed to support this theory.

As we have shown, DMSO-induced toxicity in cord blood stem cell transplantation may be a serious complication that has to be monitored. Using a lower concentration of DMSO, removing the lysed cells by washing procedures, or the reduction of infused peripheral blood stem cell transplant by CD34+ selection might reduce the risk of infusion-related toxicity. Once there is toxicity aggressive hydration, intravenous steroids and shock treatment if necessary may reverse these serious complications.

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