been initiated. Because plasma drug level positively correlates with response to alemtuzumab-containing therapy, future clinical studies of alemtuzumab-containing therapy should ideally include measurement of plasma drug concentration to evaluate the feasibility of PK-directed dosing, with the aim of improving patient response and minimizing toxicity.

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Respiratory depression and somnolence in children receiving dimethylsulfoxide and morphine during hematopoietic stem cells transplantation

Dimethylsulfoxide (DMSO) has been commonly used for the past 20 years as a well-known cryo-protectant agent. It acts by penetrating the cell and binding water molecules; by doing so, it blocks the efflux of water and prevents cellular dehydration, maintains stable pH, intracellular salt concentration, and the formation of the ice crystals which endanger cell integrity. The most common clinical application of such a procedure is the cryo-protection of stem cells frozen in liquid nitrogen for their subsequent reinfusion in autologous stem cell transplantation.[1]

The infusion of DMSO may have several side effects, such as vasoconstriction, nausea, vomiting, abdominal cramps, cardiovascular and respiratory problems, and a variety of neurological events.[2-4] Despite this, it is used by transplant specialists worldwide.

Morphine is widely used to control pain in patients with different clinical conditions. Its wider use has been repeatedly advocated by scientists, patients' associations and the media in order to combat old prejudices restricting its use to terminal cancer patients. Patients undergoing hematopoietic stem cell transplantation (HSCT) may face pain for different causes, including severe mucositis.[5] Thus the use of morphine and DMSO may concur in such patients. To our knowledge, reports of adverse events resulting from their interaction are not available.

Recently, we observed 3 patients who unexpectedly developed somnolence and clinically significant oxygen desaturation soon after reinfusion of autologous stem cells. Their main features are summarized in Table 1. Neurological alterations rarely occur as a primary complication during or soon after stem cell infusion. In a recent survey, only 3 out of 179 consecutive patients experienced neurological complications during stem cell infusion.[6] In order to understand the pathogenesis of such unexpected events, we performed a thorough critical re-evaluation of the clinical course of the patients. We noted that all of them were already receiving i.v. morphine infusion at the time of stem cell infusion; this is quite unusual in our experience, since severe pain is more frequently observed later during the course of transplantation.[5] Thus, we wondered if morphine interaction with any other transplant-related agent might

Table 1. Main features of the three patients.

	Case 1	Case 2	Case 3
Gender, age	Male, 13 years	Female, 15 years	Female, 22 years
Cancer type	Medulloblastoma	Pinealoblastoma	Medulloblastoma
Conditioning regimen	Thiotepa 900 mg/m^2, etoposide 1,500 mg/m^2	Thiotepa 900 mg/m^2, melphalan 140 mg/m^{2}mg/m^2,	Thiotepa 900 mg/m^2, etoposide 1,500 mg/m^2
Source of stem cells	Peripheral blood stem cells	Autologous bone marrow	Peripheral blood stem cells
Associated morphine dosage	20 μg/kg/h	20 μg/kg/h	20 μg/kg/h
Amount of DMSO	184 mg/kg	1,304 mg/kg	444 mg/kg
Time from stem cell infusion to onset of symptoms	12 hours	11 hours	84 hours
Type of symptoms	Somnolence, oliguria, respiratory depression, desaturation	Somnolence, respiratory depression, desaturation	Somnolence, oliguria, respiratory depression, desaturation
Treatment	O_2, morphine withdrawal	O_2, morphine tapering and withdrawal	O_2, morphine withdrawal
Outcome	Recovery within 48 hours from symptoms	Recovery within 48 hours from symptoms	Recovery within 48 hours from symptoms

have been responsible for the observed complication.

DMSO is a solvent for water-insoluble drugs, and has a well known analgesic effect.[7] In a recent report, Fossum *et al.*[8] documented in a mouse model that DMSO enhances morphine potency when the two drugs are used by microinjection into the ventro-lateral peri-aqueductal gray, a part of the descending pain modulatory system that contributes to morphine antinociception and tolerance. In our 3 patients the unexpected neurological syndrome with clinically significant oxygen desaturation may thus be explained by concurrent DMSO and morphine infusion; the clinical picture being fully reversed following morphine withdrawal. We suggest that some patients receiving morphine may be at a higher risk for DMSO-associated neurological symptoms and respiratory depression. Studies are needed to verify if infusion of lower amounts of DMSO, as achieved by reducing its concentration,[9,10] will contribute to limiting its neurotoxicity.

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