short report
Haematologica 1996; 81:59-61

FRACTIONATED INFUSIONS OF CRYOPRESERVED STEM CELLS MAY PREVENT DMSO-INDUCED MAJOR CARDIAC COMPLICATIONS IN GRAFT RECIPIENTS

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ABSTRACT

The amount of transfused dimethyl sulfoxide (DMSO) is indicated as the major cause of the cryoprotectant-related toxicity in autologous stem cell recipients, with a high incidence of major cardiac side effects. In this study we tried to discover whether fractionated infusion of the total graft volume could prevent the DMSO-related major cardiovascular side effects. We conclude that continuous cardiac monitoring during and after fractionated infusions of DMSO-containing graft documented no major arrhythmias, with only seven episodes of asymptomatic sinus bradycardia.

Key words: stem cell transplantation, DMSO, cardiac toxicity

The transfusion of cryopreserved stem cells from either bone marrow or peripheral blood has expanded rapidly for the treatment of patients with cancer.[1,2] Dimethyl sulfoxide (DMSO) is the most frequently used cryopreservation agent.[3] Autologous stem cell transplantation (ASCT) is associated with several complications, primarily due to profound cytopenia and the preparative regimens. Moreover, the infusion of cryoprotectants together with stem cells may be associated with other complications, including variations of blood pressure, dyspnea and cardiac toxicity.[4-6] The major cause hypothesized for the development of infusion-related cardiac side effects from the thawed graft is the amount of DMSO administered. Consequently, different approaches have been suggested to reduce its volume, but these are time-consuming methods and may increase the risk of reducing the actual number of stem cells infused.

Since we believe that the major cardiovascular side effects could be avoided by infusing small doses of the total DMSO volume, we report herein our experience with continuous cardiac monitoring during and after fractionated reinfusions of cryopreserved stem cells.

Patients and Methods

Patients, cryopreservation and infusion of stem cells

Twenty-two patients entered this study. Their diagnoses are indicated in Table 1. Peripheral stem cells were mobilized either by chemotherapy or G-CSF or both, while bone marrow was harvested under general anesthesia. Buffy coats, obtained after one or two cycles of hydroxyethyl-starch/graft mixture sedimentation, were resuspended for crypreservation in RPMI medium with 10% DMSO and 5% albumin, stored in freezing bags at –80°C overnight and then transferred in liquid nitrogen at –180°C. For infusion, the thawed graft was given in two to seven fractions of 1 mL/kg every twelve hours.

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Received July 14, 1995; accepted November 6, 1995.

Case No.	Age (years)	Diagnosis	Previous xRT	High dose regimen	BMSC		PBSC		Cardiac arrhythmia
					10^6/Kg	ml/Kg*	10^6/Kg	ml/Kg*	
1	36	HD	no	BEAM	411.9	4.17	234.3	2.98	-
2	36	NHL	no	BEAM	312.4	3.21	228.5	2.50	sb
3	24	NHL	yes	BEAM	292.8	3.00	232.1	2.30	-
4	23	NHL	no	BEAM	290.7	4.60	267.6	2.69	-
5	46	ANLL	no	LACE	426.2	4.60	-	-	sb [1,2]
6	27	ANLL	no	BAVC	347.7	5.90	-	-	-
7	13	ALL	no	BEAM	351.2	3.70	-	-	-
8	36	ANLL	no	LACE	316.6	3.30	066.6	0.60	sb [1]
9	25	NHL	no	BEAM	242.5	2.87	300.0	3.00	sb
10	54	ANLL	no	LACE	217.5	2.43	-	-	-
11	40	HD	no	BEAM	371.7	3.84	115.3	1.28	-
12	54	NHL	no	BEAM	188.8	2.00	266.6	2.77	sinus rhythm [3]
13	44	NHL	yes	BEAM	160.0	2.00	176.7	1.85	sb
14	54	HD	no	ETC	225.3	2.30	139.4	1.40	-
15	26	ANLL	no	LACE	304.0	3.10	-	-	-
16	56	NHL	no	BEAM	210.0	3.90	250.0	2.60	-
17	27	CML	no	LACE	358.3	4.10	-	-	-
18	17	GLIOMA	yes	ETC	232.6	2.10	473.9	4.70	sb
19	63	NHL	no	BEAM	221.5	2.20	130.6	1.70	-
20	45	NHL	no	BEAM	307.6	3.00	195.3	1.80	sb
21	36	ANLL	no	LACE	251.6	2.50	-	-	-
22	46	NHL	yes	BEAM	-	-	564.0	5.60	-

Table 1 . Patient characteristics and cardiac changes associated with graft infusions.

Legend:
BEAM: BCNU, Etoposide, Ara C, Melphalan
LACE: CCNU, Ara C, CY, Etoposide
ETC: Etoposide, Thiotepa, CY
BAVC: BCNU, m-AMSA, Etoposide, Ara C
BMSC: Bone marrow stem cells
PBSC: Peripheral blood stem cells
1. below 50 beats per minute;
2. treated with atropine;
3. bigeminy before stem-cell infusion
sb= sinus bradycardia (< 60 beats per minute).
**cryopreservant mixture volumes*

Cardiac monitoring was carried out in all patients before and during the graft infusion, and for the following six hours.

Results

The main characteristics of the patients, the type of pre-transplant conditioning regimens, the number and volume of infused stem cells and the cardiac arrhythmias are summarized in Table 1.

Pulmonary function, evaluated by spirometry, was normal in all patients. Case #12 showed a bigeminy at baseline electrocardiograms, whereas the remaining patients showed no significant impairment. At echocardiography, 4 patients were found to have a mild mitral reflux (cases #8, 10, 16 and 20), associated in one patient (case #16) with a mild enlargement of both ventricular cavities, and in another case with a mild mitral valve prolapse disease (case #1). Calculation of the left ventricular ejection fraction proved to be normal in all patients. No major arrhythmias were observed in our cases, while we documented only seven episodes (31.8%) of asymptomatic sinus bradycardia (rate ≤ 60 beats per minute). In particular, only two patients experienced heart rates < 50 beats per minute, and one of them necessitated therapy with atropine. Moreover, no significant variation of blood pressure was documented during bradycardia. Of interest, graft infusion converted the baseline bigeminy into a sinus rhythm in case #12. Later on, this patient showed again bigeminy.

Discussion

Toxicity related to graft infusion in recipients of ASCT has been widely demonstrated. Bacter-

ial contamination of processed marrows, transient hypotension or hypertension, dyspnea, nausea and emesis are the most frequent side effects observed in cryopreserved stem cell recipients.[7] Febrile reactions have also occurred, mostly due to clumped and damaged white blood cells. Increased pulse rate was demonstrated in more than half of a group of graft recipients, while 71% of them developed elevated blood pressure.[10]

More recently, a very high incidence of cardiovascular side effects with 29.4% transient heart blocks was reported after infusion of cryopreserved stem cells.[4] Consequently, approaches aimed at decreasing DMSO-related complications, such as mononuclear cell enrichment by additional separation techniques or washing the grafts before infusion, have been attempted.[5] However, these are time-consuming methods and may increase the risk of engraftment failure.

In our series of 22 patients undergoing ASCT, no one experienced major cardiovascular side effects, and only seven cases showed sinus bradycardia after the infusion of fractionated cryopreserved graft.

We conclude by suggesting that fractionated infusion of the total graft volume should be considered in order to prevent DMSO-related major cardiovascular side effects. This should also apply to allogeneic peripheral stem cell infusion.[11, 12]

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