Ann Hematol (2000) 79:523–526 

CASE REPORT

**R. Zenhäusern · A. Tobler · L. Leoncini**
**O.M. Hess · P. Ferrari**

# Fatal cardiac arrhythmia after infusion of dimethyl sulfoxide-cryopreserved hematopoietic stem cells in a patient with severe primary cardiac amyloidosis and end-stage renal failure

Received: 5 October 1999 / Accepted: 23 February 2000

**Abstract** Amyloidosis (AL) is a rapidly fatal plasma cell dyscrasia causing progressive multiorgan failure. Recently, substantial improvement of survival was reported following high-dose chemotherapy with peripheral blood stem cell (PBSC) rescue. We describe a patient with AL with severe cardiac and renal involvement who received high-dose melphalan followed by fractioned autologous PBSC transplantation (455 ml on day 1 and 350 ml on day 2). Immediately after the second infusion of the PBSCs, life-threatening cardiac arrhythmias occurred and, despite intensive treatment, the patient died less than 24 h later. The infusion of cryopreserved PBSCs may be associated with complications, including cardiac toxicity. Dimethyl sulfoxide (DMSO) is the most frequently used cryopreservation agent. In the present case, we suggest that DMSO could have played an important role in causing the fatal cardiac arrhythmias. The mechanisms of the cardiovascular effects of DMSO and the possible preventive measures are discussed. Given the poor prognosis of AL and the promising results of dose-intensive chemotherapy with autologous PBSC transplantation, careful patient selection and intensive monitoring are mandatory in order to further pursue this therapeutic approach.

**Key words** Amyloidosis · Melphalan · Peripheral blood stem cell transplantation · Dimethyl sulfoxide · Cardiac arrest

R. Zenhäusern (✉)
Department of Oncology, University of Berne, Inselspital, CH-3010 Berne, Switzerland
e-mail: reinhard.zenhaeusern@insel.ch
Tel.: +41-31-6324114
Fax: +41-31-3821237

A. Tobler · L. Leoncini
Department of Hematology, University of Berne, Switzerland

O.M. Hess
Department of Cardiology, University of Berne, Switzerland

P. Ferrari
Department of Nephrology, University of Berne, Switzerland

## Introduction

Primary amyloidosis (AL) occurs in patients with B-cell or plasma-cell dyscrasias where fragments of monoclonal immunoglobulin light chains form amyloid fibrils. Their accumulation in tissue destroys the normal structures and functions of vital organs. The organs most commonly involved are the kidneys and the heart. The disease is rapidly progressive in most patients and death usually occurs 1–2 years from diagnosis despite treatment with standard oral doses of melphalan and prednisone [1–3]. Patients with cardiac involvement and congestive heart failure have the worst prognosis, with a median survival duration of approximately 6 months [1, 3].

The association of AL with multiple myeloma suggests that high-dose chemotherapy followed by rescue with peripheral blood stem cells (PBSCs) may be beneficial in these patients [4, 5]. With this therapeutic approach, substantial improvements in amyloid-related organ disease and remission of the plasma-cell dyscrasia have been reported in selected patients with AL [2, 6–8].

We describe here a patient with cardiac and renal AL who developed severe cardiac arrhythmia culminating in cardiac arrest following infusion of cryopreserved autologous PBSCs.

## Case report

A 60-year-old man was admitted for treatment of systemic amyloidosis. He was well until 3 months before, when he began to experience dyspnea upon exertion, progressive fatigue, and weakness. Right-sided cardiac failure, Bence-Jones proteinuria, and renal insufficiency suggested the diagnosis of AL, which was confirmed by rectal biopsy. Upon clinical examination, the blood pressure was 100/70 mmHg, and there was mild peripheral edema. No lymphadenopathy, hepatomegaly, or peripheral neuropathy were found. A complete blood cell count showed no abnormality. Serum creatinine was 338 μmol/l, urea 17.6 mmol/l, uric acid 563 μml/l, and lactate dehydrogenase (LDH) 600 U/l. The

other results of blood chemistry [sodium, potassium, calcium, protein, albumin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), bilirubin, and alkaline phosphatase] were normal. Serum-immunoelectrophoresis revealed a monoclonal immunoglobulin light chain peak of the lambda type. Free monoclonal light chains were also detectable in the urine (0.1 g/day) on a total protein loss of 0.24 g/day. Bone marrow examination revealed 10% plasma cells predominantly expressing lambda light chain isotypes. A chest x-ray revealed bilateral, predominantly right-sided pleural effusion. An electrocardiogram (ECG) showed normal cardiac rhythm with a rate of 80 bpm, first-degree atrioventricular block (AV-block), right bundle branch block (RBBB), and nonspecific T-wave abnormalities. An echocardiogram revealed granular sparkling of the myocardium with a ventricular septal wall of 15 mm and signs of restrictive cardiomyopathy with diastolic dysfunction but normal left ventricular systolic function (ejection fraction 70%). These findings were confirmed using cardiac catheterization. Left ventricular end-diastolic pressure was 25 mmHg, and left ventricular ejection fraction was 83%. Endomyocardial biopsy showed diffuse amyloid deposition.

PBSCs were mobilized with granulocyte colony-stimulating factor at a dose of 10 μg/kg by subcutaneous injection for 5 days. Daily large-volume leukapheresis was performed between day 6 and day 8 and $3.5 \times 10^6$ CD34+ cells/kg were collected, frozen in a controlled rate freezer with dimethyl sulfoxide (DMSO) as cryoprotectant, and stored in liquid nitrogen. Before freezing, the buffy coats of the PBSC samples were mixed with the cryoprotectant and dextrane, resulting in a final concentration of 5% DMSO.

During the following weeks, the patient was treated with furosemide only. Cardiac function remained stable, but progressive renal failure required hemodialysis twice weekly. High-dose chemotherapy was started 3 weeks after PBSC collection, with melphalan administered intravenously over a 60-min period at a dose of 200 mg/m$^2$ on day 0. This was well tolerated. The patient was then transferred to the intensive care unit (ICU) to allow continuous ECG monitoring during and after infusion of PBSCs. Hemodialysis was performed 20 h after chemotherapy. PBSCs were transfused in two fractions 24 h and 48 h after chemotherapy. Each bag of cryopreserved PBSCs was thawed in a water bath at 37 C, immediately drawn into a syringe, and injected intravenously through a central venous catheter over a period of 40 min. The patient was premedicated intravenously with methylprednisolone (125 mg). The first fraction of PBSCs was given in a volume of 455 ml, containing $2.33 \times 10^6$/kg CD34+ cells. The second fraction contained a volume of 350 ml and $0.73 \times 10^6$/kg CD34+ cells. Until day 2, cardiac function was stable, no arrhythmias occurred, electrolytes were within normal limits, and fluid balanced by hemodialysis as needed. On the day of the second PBSC transfusion, the patient felt good; however, at the end of the PBSC infusion, abrupt life-threatening sinus bradycardia developed (minimal heart rate 20 bpm). Rapid resuscitation resulted in restoration of normal pulse and blood pressure. Hemodialysis treatment was started immediately after this event. At this time, there was no evidence of fluid overload, myocardial infarction, or pulmonary embolism. The levels of serum electrolytes were found to be within normal limits with no significant changes when compared with values before the second PBSC infusion (Table 1). The PBSC infusions, combined, contained a total amount of 48 g DMSO. Osmolality was 1235 mosmol/l, and the total amount of potassium administered during the second PBSC transfusion was 2.8 mmol.

A temporary pacemaker was inserted through the jugular vein. After a short, stable phase, sinus bradyarrhythmias recurred followed by several episodes of ventricular tachycardia. The onset of the latter occurred after the infusion of epinephrine to treat the bradycardia. Despite maximal treatment, the patient died 20 h after the onset of the first arrhythmias due to cardiac arrest from electromechanical uncoupling.

A post-mortem examination revealed chronic pulmonary edema, bilateral pleural effusions (right: 1100 ml; left: 200 ml), and ascites. The heart weighed 660 g (normal $<350$ g). Microscopic examination showed large amounts of amyloid in the heart and the kidneys.

## Discussion

AL, a plasma-cell dyscrasia causing progressive multiorgan dysfunction, is rapidly fatal in the majority of patients [1–3]. Treatment with alkylating agents is used to decrease or eradicate the amyloigenic plasma-cell clone, producing the immunoglobulin light chain in the bone marrow. Current therapeutic strategies show only modest improvements in the dismal prognosis of this condition [3, 9]. Treatment failure is mainly due to the relative resistance of the malignant plasma-cell clone to chemotherapy, and because the diagnosis is frequently made late in the disease course. High-dose chemotherapy with autologous PBSC support is widely used in hematologic malignancies and some solid tumors. Currently, 200 mg/m$^2$ melphalan administered intravenously, followed by PBSC transplantation is routinely given to patients with multiple myeloma with low toxicity [4, 5]. In an attempt to eradicate the pathologic plasma-cell clone in patients with AL, some clinical trials using this therapeutic approach have been conducted. Preliminary reports show promising results with a substantial percentage of patients achieving good clinical response and elimination of abnormal marrow plasma cell infiltrates as well as suppression of serum or urinary light chains [6–8]. Pleural effusion in patients with cardiac amyloidosis has been reported recently to be a contraindication for high-dose melphalan [7]; however, at the time our patient was treated, this fact was not yet known.

In the present case, we report on a patient with biopsy-proven AL and clinical significant involvement

**Table 1** Blood chemical values. *PBSCT* peripheral blood stem cell transplantation

| Variable | Normal range | Upon admission | Before second PBSCT | 15 min After second PBSCT | 4 h After second PBSCT |
|---|---|---|---|---|---|
| Sodium (mmol/l) | 132–142 | 136 | 132 | – | 134 |
| Potassium (mmol/l) | 3.5–4.7 | 4.8 | 5.2 | 4.8 | 3.7 |
| Calcium (mmol/l) | 2.10–2.55 | 2.4 | 2.74 | 2.05 | 2.23 |
| Phosphate (mmol/l) | 0.74–1.55 | 1.57 | – | 2.89 | 1.58 |
| Creatinine (μmol/l) | 59–116 | 295 | 351 | – | – |

not only of the heart, but also of the kidney. Given the rapid progression and the poor prognosis of the disease, we decided to treat the patient with high-dose melphalan with PBSC transplantation. On day 2, immediately after transfusion of the second fraction of PBSCs, severe fatal bradyarrhythmia occurred.

High-dose chemotherapy with PBSC transplantation can be associated with severe complications, mostly resulting from the intensive cytotoxic preparative regimen and profound bone marrow aplasia. The infusion of autologous marrow or PBSCs is generally well tolerated and considered safe. Only a few reports have discussed the adverse reactions in patients transfused with cryopreserved cells [10–13]. However, transient sinus bradycardia (49–65%), second-degree heart block (10–24%), and even complete heart block (5–6%) are seen during PBSC infusions [10, 12, 14]. In a few patients, severe and life-threatening cardiopulmonary events did occur [15].

Several factors might have contributed to the fatal cardiac complication in the patient in this study. His age and multiorgan dysfunction seem to be important risk factors for the transplant-related complications. Although echocardiography showed preserved left ventricular systolic function, there was a severe cardiac amyloidosis, including conduction defect in the ECG (AV-Block, RBBB) consistent with previous reports [16]. In addition, the patient had end-stage renal disease. Melphalan-induced arrhythmia should be considered as a possible precipitating event, although to date, only atrial fibrillation has been described to occur after high-dose melphalan [17]. Several possible causes, such as electrolyte imbalance, acute volume expansion, toxic effects of cell lysis products, temperature of the infusate, and adverse effects of cryoprotectants, could be responsible for the development of cardiac arrhythmias after PBSC transplantation [10, 12, 18]. In our patient, electrolytes were within normal limits immediately after the end of the PBSC infusion. Although the total volume of PBSCs was large compared with current standard [13], it was given in two fractions on two separate days in a patient with residual diuresis of 1000 ml/day. Thus, acute volume overload does not seem to represent a major issue in terms of fluid volume per se. Dialysis support avoided fluid overload previous to the PBSC transfusion, but given the hyperosmolality of the 350 ml DMSO infusate, rapid expansion of the intravascular volume could have contributed to the cardiac decompensation. Hemodialysis was again initiated just after the initial successful cardiopulmonary resuscitation (CPR) attempt, but did not prevent the later onset of arrhythmias. Concomitant effects from the infusion of cell lysis products cannot be excluded, although the apheresis product was ficoll-separated before freezing. An association between the temperature of the infusate and the occurrence of arrhythmias is very unlikely, because the cryopreserved PBSCs were thawed in a water bath at 37 C.

The most likely culprit, albeit hypothetical, is the cryopreservation agent, DMSO. A possible cause hypothesized for the development of infusion-related cardiac side effects is the amount of DMSO in this patient with end-stage renal failure [19]. DMSO is known to liberate histamine and cause degranulation of mast cells [20] and has been shown to exert negative chronotropic effects on heart tissue in animal models. It might be mediated by both direct (muscular) and indirect (neural) mechanisms. Sams et al. showed that 0.6–6% DMSO strikingly depressed the response of the diaphragm to both muscle and nerve electrical stimulation via inhibition of cholinesterase activity [21]. A direct nerve blocking effect of DMSO was also demonstrated by a 40% decrease in conduction velocity of the sciatic nerve after immersion in 6% DMSO [22]. However, the relevant cardiovascular effects of DMSO remain controversial. DMSO toxicity in animals with normal renal function is low [23, 24]. The $LD_{50}$ of an oral dose in rats is approximately 14.5 g/kg. A total dose of 42 g/kg administered orally over 14 days in rhesus monkeys did not result in the death of the animals [23], as did a rapid infusion of 1 g/kg in horses [24]. Major side effects were neuromuscular abnormalities, hemolysis, and hemoglobinuria. Upon histologic examination, no signs of central nervous system or renal tubular damage were found. Unfortunately, no data are available regarding the toxicity in uremic animals. Ravid et al. did not report any fatalities in 13 humans with renal dysfunction due to amyloidosis and treated with 7–15 g/d oral DMSO for up to 16 months [25]. Among these patients, there were three subjects with primary amyloidosis, two of which had end-stage renal disease. DMSO treatment did not have any influence either on renal function or the general conditions of the patients [25]. However, considering the pharmacokinetic properties of DMSO and its metabolite dimethyl sulfone ($DMSO_2$), it seems possible that, in our patient, a cumulation of the DMSO could have occurred between the first and the second PBSC infusion. In non-uremic subjects, the volume of distribution of DMSO is about 36 l, and the half-life of DMSO is 16 h. The half-life of $DMSO_2$ in these subjects is 38 h [26]. Urinary excretion of DMSO and $DMSO_2$ are 44% and 4%, respectively. Because of the high protein binding of DMSO, dialysability is poor, so that the cumulative dose of 48 g DMSO administered within 24 h, corresponding to 0.8 g/kg, may have been too high and caused cardiac toxicity.

Although the precise mechanism responsible for the severe bradyarrhythmia described in this report cannot be fully clarified, the close sequence of events leading to irreversible cardiac arrest suggest a toxicity of one of the components of the PBSC transplantation. We think that DMSO and volume expansion played a major role in our patient's unfortunate outcome. The presence of severe baseline cardiac dysfunction probably rendered our patient sensitive to any changes of the above mechanisms. Removal of DMSO or lysed cells by washing procedures, or the reduction of infused PBSC trans-

plant by CD34 positive selection might reduce the risk of infusion-related toxicity. Given the poor prognosis of AL and the promising preliminary results of dose-intensive chemotherapy with PBSC transplantation, we do not advise against pursuing this therapeutic approach. Nevertheless, patients with amyloid-related multiorgan dysfunction must be carefully selected for this treatment.

## References


1. Kyle RA, Gertz MA (1995) Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 32:45–59
2. Falk RH, Comenzo RL, Skinner M (1997) The systemic amyloidosis. N Engl J Med 337:898–909
3. Gertz MA, Kyle RA, Greipp PR (1991) Response rates and survival in primary systemic amyloidosis. Blood 77:257–262
4. Attal M, Harousseau J-L, Stoppa A-M, Sotto J-J, Fuzibet J-G, Rossi J-F, Casassus P, Maisonneuve H, Facon T, Ifrah N, Payen C, Bataille R. A (1996) Prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 335:91–97
5. Jagannath S, Vesole DH, Glenn L, Crowley J, Barlogie B (1992) Low risk intensive therapy for multiple myeloma with combined autologous bone marrow and blood stem cell support. Blood 80:1666–1672
6. Comenzo RL, Vosburgh E, Simms RW, Bergethon P, Sarnacki D, Finn K, Dubrey S, Faller DV, Wright DG, Falk RH, Skinner M (1996) Dose-intensive melphalan with blood stem cell support for the treatment of AL amyloidosis: one-year follow-up in five patients. Blood 88:2801–2806
7. Comenzo RL, Vosburgh E, Falk RH, Sanchorawala V, Reisinger J, Dubrey S, Dember LM, Berk JL, Akpek G, LaValley M, O'Hara C, Arkin CF, Wright DG, Skinner M (1998) Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. Blood 91:3662–3670
8. Moreau P, Milpied N, de Faucal P, Petit T, Herbouiller P, Bataille R, Harousseau JL (1996) High-dose melphalan and autologous bone marrow transplantation for systemic AL amyloidosis with cardiac involvement. Blood 87:3063–3064
9. Merlini G (1995) Treatment of primary amyloidosis. Semin Hematol 32:60–79
10. Davis JM, Rowly SD, Braine HG, Piantadosi S, Santos GW (1990) Clinical toxicity of cryopreserved bone marrow graft infusion. Blood 75:781–786
11. Kessinger A, Schmit-Pokorny K, Smith D, Armitage J (1990) Cryopreservation and infusion of autologous peripheral blood stem cells. Bone Marrow Transplant 5[suppl 1]:25–27
12. Keung Y-K, Lau S, Elkayam U, Chen S-C, Douer D (1994) Cardiac arrhythmia after infusion of cryopreserved stem cells. Bone Marrow Transplant 14:363–367
13. Alessandrino EP, Bernasconi P, Caldera D, Colombo A, Bonfichi M, Malcovati L, Klersy C, Martinelli G, Maiocchi M, Pagnucco G, Varettoni M, Perotti C, Bernasconi C (1999) Adverse events occurring during bone marrow or peripheral blood progenitor cell infusion: analysis of 126 cases. Bone Marrow Transplant 23:533–537
14. Styler MJ, Topolsky DL, Crilley PA, Covalesky V, Bryan R, Bulova S, Brodsky I (1992) Transient high grade heart block following autologous bone marrow infusion. Bone Marrow Transplant 10:435–438
15. Rapoport AP, Rowe JM, Packman CH, Ginsberg SJ (1991) Cardiac arrest after autologous marrow infusion. Bone Marrow Transplant 7:401–403
16. Reisinger J, Dubrey SW, Lavalley M, Skinner M, Falk RH (1997) Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement. J Am Coll Cardiol 30:1046–1051
17. Olivieri A, Corvatta L, Montanari M, Brunori M, Offidani M, Ferretti GF, Centanni M, Leoni P (1998) Paroxysmal atrial fibrillation after high-dose melphalan in five patients autotransplanted with blood progenitor cells. Bone Marrow Transplant 21:1049–1053
18. Stroncek DF, Fautsch SK, Lasky LC, Hurd DD, Ramsay NKC, McCullough J (1991) Adverse reactions in patients transfused with cryopreserved marrow. Transfusion 31:521–526
19. Yellowless P, Greenfield C, McIntyre N (1980) Dimethylsufphoxide-induced toxicity. Lancet 2:1004–1006
20. Klingman A (1965) Topical pharmacology and toxicology of dimethyl-sulfoxide – part 1. J Am Med Assoc 193:140–145
21. Sams WM, Carrol NV, Crantz PL (1966) Effects of dimethylsulfoxide on isolated innervated skeletal smooth muscle and cardiac muscle. Proc Soc Exp Biol Med 122:103–107
22. Sams WM (1967) The effects of dimethyl sulfoxide on nerve conduction. Ann N Y Acad Sci 141:242–247
23. Layman DL, Jacob SW (1985) The absorption, metabolism and excretion of dimethyl sulfoxide by rhesus monkeys. Life Sci 37:2431–2437
24. Blythe LL, Craig AM, Christensen JM, Appel LH, Silzeski ML (1986) Pharmacokinetic disposition of dimethyl sulfoxide administered intravenously in horses. Am J Vet Res 47:1739–1743
25. Ravid M, Shapira J, Lang R, Kedar I (1982) Prolonged dimethyl sulfoxide treatment in 13 patients with systemic amyloidosis. Ann Rheum Dis 41:587–592
26. Egorin MJ, Rosen DM, Sridhara R, Sensenbrenner L, Cottler-Fox M (1998) Plasma concentrations and pharmacokinetics of dimethylsulfoxide and its metabolites in patients undergoing peripheral-blood stem-cell transplants. J Clin Oncol 16:610–615