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Multi-organ involvement: lessons from the experience of one victim of the Tokai-mura criticality accident

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Abstract. Allogeneic placental umbilical cord blood cell transplantation after a short regimen of antithymocyte globulin followed by extensive use of various haematopoietic factors was performed urgently on demand to one of the victims of the JCO Co. Ltd criticality accident of Tokai-mura for the treatment of severe bone marrow failure. After forming a donor/recipient mixed chimera for a short period without causing graft-versus-host disease, the recipient's own haematopoietic cells recovered gradually toward 50 days after transplantation, as expected. However, the functions of the recovered autologous lymphocytes were observed to be severely impaired. After 210 days the patient died of severe opportunistic infections together with late onset non-haematological tissue damage. Our experience indicated that preservation of life without curing the radiation-induced irreversible lymphocyte damage and non-haematological tissue damage would not be possible even if severe transient bone marrow failure was overcome.

Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) has been considered as an acceptable therapeutic modality for severely damaged bone marrow functions. However, its feasibility and efficacy in cases of accidentally irradiated individuals remain to be established. In fact, in the latest radiation accident at the Chernobyl nuclear power plant, 13 victims received allogeneic bone marrow transplants and 7 victims received fetal liver cell transplants, but only 2 of the 13 bone marrow recipients who rejected the grafts following autologous bone marrow recovery were reported to survive long term [1, 2]. Our concerns in advance of HSCT are how to shorten the pancytopenic phase, how to reduce additional toxicities associated with HSCT, such as the regimen-related toxicities and graft-versus-host disease (GVHD), and how to accelerate the autologous haematopoietic recovery. We have recently treated one of the victims of the Tokai-mura criticality accident by placental umbilical cord blood cell transplantation (PUCBT). This paper is a case report of this precious experience [3–6].

Background

Criticality accident

A criticality accident occurred at the uranium fuel processing plant of JCO Co. Ltd in Tokai-mura, Ibaragi Prefecture, Japan on 30 September 1999. The accident was caused by poor working practice, namely having poured much uranium fuel from a bucket into the participation tub. Three JCO workers who actually engaged in this unsafe work were exposed non-uniformly to high radiation doses.

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Radiation exposure

One of the workers was a 39-year-old male who was pouring the fuel from the upper row of a ladder. The type of irradiation he was exposed to was mainly fast neutrons mixed with γ-rays and non-uniform irradiation. His initial symptoms of nausea and vomiting occurred almost an hour after the exposure, assuming that his dose of radiation exposure was 6–8 GyEq according to the International Atomic Energy Agency criteria. Several hours later, he was sent to the National Radiation Research Center to commence the initial treatment of daily administration of granulocyte colony-stimulating factor (G-CSF) and antibiotics in a laminar air flow room, and for estimating the dose of radiation exposure more accurately. His white blood cell count was 12 700 per mm^3, with a lymphocyte count of only 1%. The exposure dose was estimated to be approximately 6–10 GyEq based on four parameters: the initial presence of nausea and vomiting; the change in peripheral blood components; the result of chromosomal analysis of blood cells; and the amount of radioactive ^{24}Na using blood samples.

Results

Pre-transplant haematological changes

4 days after the exposure, the patient was transferred from the National Radiation Research Center to our hospital at the Institute of Medical Sciences, University of Tokyo, for examination for validity of receiving HSCT. It was observed that his lymphocyte count reached zero by 7 days after exposure and also that his platelet count was decreasing linearly from 5 days after exposure, to less than 50 000 per mm^3 within 10 days. Additionally, his blood granulocyte count together with his bone marrow nucleated cell number decreased progressively in a short period despite the daily G-CSF injections (Figure 1). These findings indicated that he had severe impairment

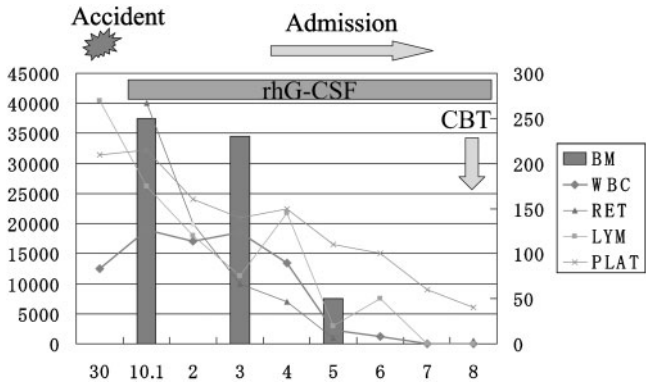

Figure 1. Changes in haematological data pre transplant. BM, bone marrow; WBC, white blood cells; RET, reticulocytes; LYM, lymphocytes; PLAT, platelets; rhG-CSF, recombinant human granulocyte-colony-stimulating factor; CBT, cord blood transplantation.

of haematopoiesis, and we decided to perform urgent rescue of haematopoiesis by PUCBT.

Performance of allogeneic PUCBT

The conditioning regimen for PUCBT consisted of antithymocyte globulin (ATG) (2.5 mg per kg for 2 consecutive days), and GVHD prophylaxis consisted of the combined use of cyclosporine A (CyA) and methylprednisolone (mPSL). HLA-DRB1 locus mismatched unrelated placental umbilical cord blood (PUCB) (2.08×10^7 total nucleated cells per kg) obtained from Japan Cord Blood Bank Network was transplanted on 9 October 1999 (10 days after the exposure). G-CSF, erythropoietin (EPO) and thrombopoietin (TPO) were concurrently administered to accelerate haematopoietic recovery (Figure 2). The granulocyte count rose to more than 500 per mm^3 on day 15 after PUCBT. Donor/recipient mixed chimerism, confirmed by chromosomal

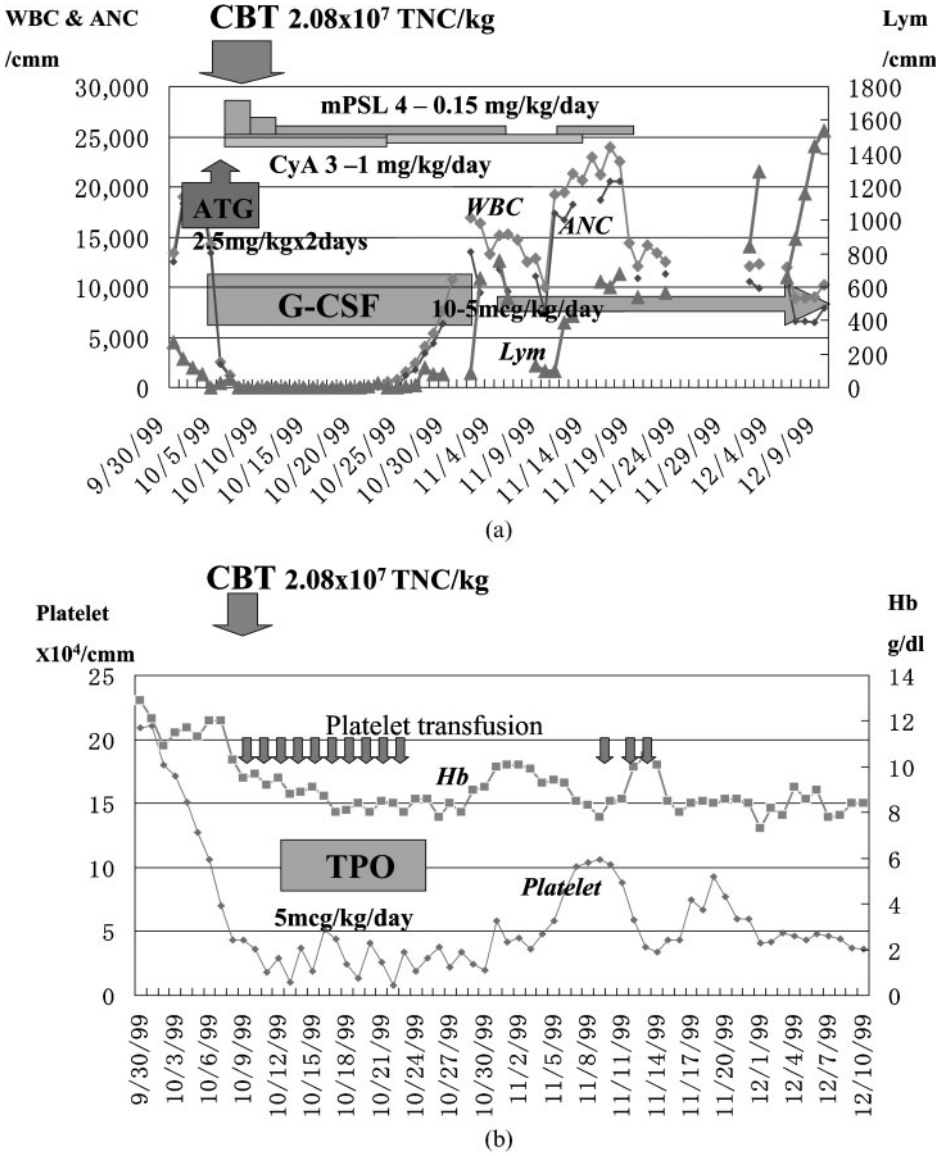

Figure 2. Clinical course post transplant: changes in (a) blood leukocyte numbers and (b) haemoglobin level and blood platelet numbers. WBC, white blood cells; ANC, absolute neutrophil count; CBT, cord blood transplantation; TNC, total nucleated cell count; mPSL, methylprednisolone; CyA, cyclosporine A; ATG, antithymocyte globulin; G-CSF, granulocyte colony-stimulating factor; Lym, lymphocytes; Hb, haemoglobin; TPO, thrombopoietin.

analysis and fluorescence-labelled *in situ* hybridisation technique with Y-chromosome-specific probes, was attained at engraftment. We reduced the dose of CyA and mPSL gradually to avoid GVHD and undesirable immunosupression. Autologous haematopoietic recovery was completed by day 50 after PUCBT. However, the recovered autologous bone marrow cells showed complex chromosomal abnormalities (Table 1).

Post-transplant immunological functions [6]

Post transplant, relatively higher percentages of $CD45RA^+$-naïve T-cells were documented, and interferon-γ (IFN-γ) producing/interleukin-4 (IL-4) non-producing staining $CD4^{bright}$ helper T-cells were dominant. Concurrent with the autologous recovery, marked proliferation of $CD3^+CD56^+$ natural killer (NK) T-cells and $CD3^-CD56^+$ NK cells was recognised on day 48 after PUCBT, suggesting that cellular immune responses were activated at this stage. Interestingly, the IFN-γ-producing cell population was transiently activated concomitant with the autologous recovery. These findings indicate the existence of the helper T-cell subtype 1-dominant Th1/Th2 axis.

We also detected transcriptional expression of granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-4, IL-6, IL-12 p40, IL-12 p35, IFN-γ and tumour necrosis factor-α (TNF-α) messenger RNA after stimulation with phorbol myristate acetate (PMA) and ionomycin (IoM) by the reverse transcriptase-polymerase chain reaction (RT-PCR) method. However, these were not different from those of the healthy volunteer donor.

On the other hand, the victim's T-cells did not respond to phytohaemagglutinin (PHA) or concanavalin-A (ConA), suggesting that his cellular immune responses were severely damaged. Similar unresponsiveness of his peripheral blood mononuclear cells was also shown in allo-mixed leukocyte reaction against HLA-DRB1 disparate unrelated healthy volunteer donor cells. His endogenous immunoglobulin (Ig)-producing capacity, measured as IgA and IgM levels in serum, was suppressed until 120 days after transplantation, but transiently increased in concordance with autologous haematopoietic recovery.

Clinical deterioration

Transient reactivation of cytomegalovirus (CMV) was detected by CMV antigenaemia analysis with CMV-specific mouse monoclonal antibodies and by CMV polymerase chain reaction of the patient's plasma. The CMV infection appeared to be successfully treated by administration of gancyclovir in addition to his concurrently increased $CD8^+$ lymphocyte count. Unfortunately, however, radiation burns of the face, throat and extremities worsened in conjunction with autologous haematopoietic recovery (Figures 3 and 4) Allogeneic cadaver skin transplantation restored the skin to some degree, but not the mucosal barriers, resulting in colonisation of methicillin-resistant *Staphylococcus aureus* on his throat despite use of vancomycin plus arbekacin. The patient suffered from obstructive sleep apnoea syndrome caused by a blood clot in the oral cavity. The patient died of aspiration pneumonia and acute respiratory distress syndrome 210 days after the accident.

Table 1. Chromosomal abnormalities of recovered autologous bone marrow cells

46, XY, add(4)(q21)	1/20
46,XY,?t(13;20)(p10;q10)	1/20
46,XY, -2,-4,+2mar	1/20
46,XY,-2,-8,+2mar	1/20
46,XY,t(1;11)(p36;p11),add(6)(q13),add(11)(p11)	1/20
46,XY,-1,-4,-6,add(9)(p24),-10,+4mar	1/20
46,XY,-4,-96,-9,-14,+5mar	1/20
46,XY,add(1)(q32),-2,add(3)(p13),add(10)(q22), add(12)(q24),-15,+2mar	1/20
45,X,-Y-4,-6,-7,+3mar	1/20
92,XXYY,add(4)(q21)X2,-7,-7,-8,+10,-12, -12,-14,-14,-20,+7mar	1/20
46,XY	3/20
36,XX,inv(9)(p11;q13)	6/20

Discussion

In this case, we decided to perform allogeneic HSCT as early as possible because early recovery of the patient's autologous bone marrow could not be expected. The haematopoietic stem cell source selected was PUCB. This was because we knew that the incidence of severe GVHD in PBCBT is low and that a quick supply of PUCB is possible from the newly established public cord blood bank network in our country [7–10]. We also used ATG alone as a conditioning regimen, and brief administration of immune suppressive agents post transplant to avoid additional tissue damage, as well as the haematopoietic factors G-CSF, EPO, TPO and GM-CSF extensively for accelerating haematopoietic recovery. As a result, early and transient haematopoietic recovery with desirable donor/recipient mixed chimerism [11] was achieved around 10 days after transplantation, and then autologous cells began to increase towards day 50 after transplantation when autologous recovery was complete. However, from around this time, the number of peripheral blood cells did not reach normal levels and the immune functions of the recovered autologous cells were found by *in vitro* tests to be markedly suppressed together with having severely damaged chromosomes. Our experience tells us that preservation of life would be very difficult if damage

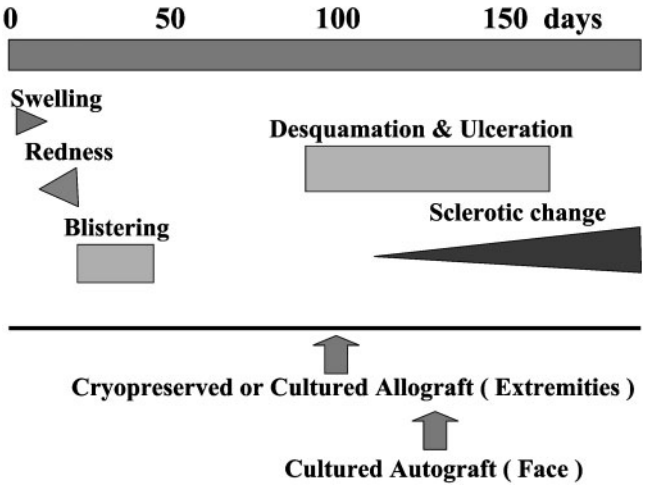

Figure 3. Time-scale of onset of tissue damage and skin transplantation.

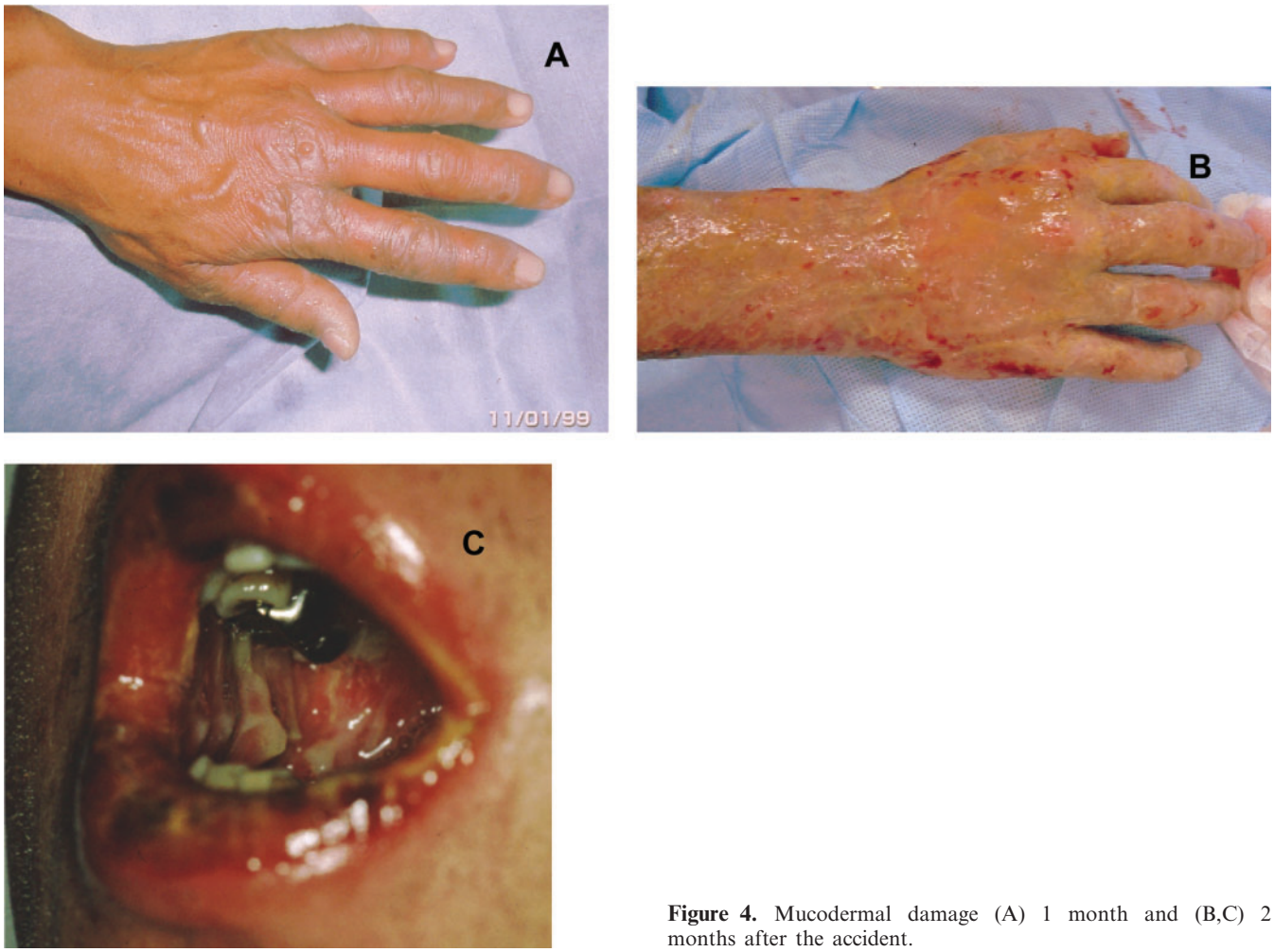

Figure 4. Mucodermal damage (A) 1 month and (B,C) 2 months after the accident.

to the immune system is advanced, although emergency treatment of severe marrow failure is possible by HSCT.

Acknowledgment

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References

1. Baranov A, Gale RP, Guskova A, et al. Bone marrow transplantation after the Chernobyl nuclear accident. N Engl J Med 1989;321:205–12.
2. International Atomic Energy Agency. Diagnosis and treatment of radiation injuries, Safety reports series No. 2. Vienna, Austria: IAEA, 1998.
3. Nagayama H, Takahashi TA, Misawa K, et al. Case presentation of worker B. In: Proceedings of International Symposium on the Criticality Accident in Tokaimura: Medical Aspects of Radiation Emergency. Chiba, Japan: National Institute of Radiological Science, 2001:154–8.
4. Iseki T, Nagayama H, Ooi J, et al. Unrelated cord blood transplantation for a heavily irradiated patient. In: Proceedings of International Symposium on the Criticality Accident in Tokaimura: Medical Aspects of Radiation Emergency. Chiba, Japan: National Institute of Radiological Science 2001:220–7.
5. Nagayama H, Misawa K, Tanaka H, et al. Transient hematopoietic stem cell rescue using umbilical cord blood for a lethally irradiated nuclear accident victim. Bone Marrow Transplant 2002;29:197–204.
6. Nagayama H, Ooi J, Tomonari A, et al. Severe immune dysfunction after lethal neutron irradiation in a JCO nuclear facility accident victim. Int J Hematol 2002;76:157–64.
7. Tomonari A, Iseki T, Ooi J, et al. Cytomegalovirus infection following unrelated cord transplantation for adult patients: a single institute experience in Japan. Br J Haematol 2003;121:304–11.
8. Ooi J, Iseki T, Takahashi S, et al. Unrelated cord blood transplantation for adult patients with advanced myelodysplastic syndrome. Blood 2003;101:4711–3.
9. Tomonari A, Iseki T, Takahashi S, et al. Varicella-zoster virus infection in adult patients after unrelated cord blood transplantation: a single institute experience in Japan. Br J Haematol 2003;122:802–5.
10. Takahashi S, Iseki T, Ooi J, et al. Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematologic malignancies. Blood 2004;104:3813–20.
11. Hill RS, Peterson FB, Storb R, et al. Mixed hematologic chimerism after allogeneic marrow transplantation for severe aplastic anemia is associated with a higher risk of graft rejection and a lessened incidence of acute graft-versus-host disease. Blood 1986;67:811–6.