Stem Cell Transplantation

High incidence of cytomegalovirus reactivation in adult recipients of an unrelated cord blood transplant

This retrospective analysis of cytomegalovirus (CMV)-seropositive adult transplant recipients showed that CMV antigenemia occurred after transplantation in 10/10 (100%) recipients of unrelated cord blood, 17/39 (43%) recipients of a related matched donor graft, 16/23 (79%) recipients of an unrelated matched donor graft, and 8/12 (67%) recipients of a mismatched related donor graft. These results suggest that unrelated cord blood transplantation itself may be correlated with a high incidence of CMV reactivation.

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Cytomegalovirus (CMV) infection is still a major concern following allogeneic hematopoietic transplantation because CMV pneumonia is fatal in 70% of patients, even when treated with a combination of antiviral therapies and CMV hyperimmune immunoglobulin.[1] Allogeneic cord blood transplantation, especially from unrelated donors, has progressively gained favor as treatment for patients with both malignant and non-malignant disorders.[2-4] As compared to allogeneic bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT), advantages of unrelated cord blood transplantation (UCBT) include ease and safety of cell collection, low risk of transmitting viral infections, prompt availability of stem cells, and reduced incidence and severity of graft-versus-host disease (GVHD).[2-4] The reduction of GVHD after UCBT is likely due to the naïve state of cord blood lymphocytes and the low cytotoxic capacity of cord blood T cells.[5] However, such immunological immaturity after UCBT can place a patient at risk of early infectious complications, accounting for most transplant-related deaths, especially in adults.[1,6] We have observed that patients undergoing UCBT appear to be at increased risk of CMV infection.

Ninety-one consecutive adult patients who were CMV-seropositive and received non-T-cell-depleted allogeneic transplants at the Kanazawa University Hospital between April 1999 and April 2004 were eligible for inclusion in this study to evaluate CMV reactivation in transplant recipients. Written informed consent was obtained from all patients. Six patients died of regimen-related toxicities before engraftment and one developed primary graft rejection followed by autologous hematopoietic recovery. The remaining 84 patients had successful initial engraftment and were included in the analysis. The patients' characteristics are given in Table 1.

CMV antigenemia assays were carried out as previously described.[7,8] In brief, heparinized blood samples were fractionated by dextran sedimentation. Slides were prepared in duplicate after cytocentrifugation; 1.5×10^5 leukocytes were fixed with formaldehyde and stained with HRP-C7 monoclonal antibodies that specifically bind the pp65 antigen of CMV (Teijin, Tokyo, Japan). The degree of CMV antigenemia was expressed as the number of CMV antigen-positive cells per 5×10^4 leukocytes. For the evaluation of CMV antigenemia, 5×10^4 leukocytes were

Table 1. Patients' characteristics.

Characteristics	Stem cell donor			
	HLA identical sibling	*HLA matched unrelated donor*	*HLA mismatched relative*	*Unrelated CB*
No. of patients	39	23	12	10
Sex, male/female	23/16	10/13	5/7	6/4
Median age (range), years	53 (14-69)	36 (17-54)	43 (15-58)	61 (15-69)
Disease				
Acute myelogenous leukemia	9	6	0	2
Acute lymphoblastic leukemia	4	6	6	2
Chronic myeloid leukemia	3	4	2	0
Myelodysplastic syndrome	6	2	0	1
Non-Hodgkin's lymphoma	7	3	3	1
Severe aplastic anemia	4	2	1	1
Myelofibrosis	1	0	0	0
Renal cell carcinoma	4	0	0	3
Osteosarcoma	1	0	0	0
Standard risk/advanced risk*	18/21	14/9	3/9	1/9
Stem cell source				
PBSC/BM	33/6	0/23	10/2	0/0
HLA disparity				
0/1/2/3	39/0/0/0	23/0/0/0	0/2/6/3/1	3/1/6/0
CMV-seropositive donor	35	22	11	0
Prior transplantation	4	2	1	5
Conditioning regimen				
Myeloablative/Reduced-intensity	15/24	18/5	7/5	1/9
GVHD prophylaxis				
CSP-based/FK506-based	38/1	11/11	7/5	7/3
Use of ATG	5	3	2	1
Use of steroids	13	4	8	6
Use of MMF	3	0	5	5
Survival >100 days, %	92	87	75	78
Survival >365 days, %	82	83	40	56

*PBSC, peripheral blood stem cell; BM, bone marrow; CB, cord blood; CSP, cyclosporine; FK506, tacrolimus; MMF, mycophenolate mofetil. *Acute leukemia in first remission, chronic myeloid leukemia in the first chronic phase, myelodysplastic syndrome with refractory anemia or refractory anemia with ringed siderblasts, malignant lymphoma in any remission, and aplastic anemia were defined as standard-risk diseases. All other patients were classified as having advanced disease.*

Table 2. Acute GVHD and CMV infection according to stem cell source.

	Stem cell source			
	HLA-identical sibling	*HLA-matched unrelated donor*	*HLA-mismatched relativedonor*	*Unrelated CB*
II-IV acute GVHD	14/39 (36)	8/23 (35)	8/12 (67)	5/10 (50)
CMV antigenemia (%)	17/39 (44)	16/23 (70)	8/12 (67)	10/10 (100)
Days between transplantation and first antigenemia, median (range)	43 (20-99)	29 (18-47)	38.5 (5-95)	32.5 (0-42)
Days between final and first antigenemia, median (range)	14 (1-117)	21.5 (0-80)	94 (0-161)	60 (7-104)
Peak no. of CMV-positive cells among $5x10^4$ leukocytes, median (range)	10 (1-395)	8 (1-714)	15 (4-250)	46 (7-543)
CMV disease (%)	1/39 (3)	1/23 (4)	0/12 (0)	1/10 (10)
Late CMV antigenemia (%)	3/36 (9)	1/19 (5)	5/9 (56)	3/7 (43)

always analyzed, because the detection limit was one CMV antigen-positive cell per 5×10^4 leukocytes in this assay.[7,8] CMV antigenemia was defined as ≥1 antigen-positive cell.[7,8] For the diagnosis of CMV disease, such as pneumonia, gastroenteritis, retinitis, and hepatitis, the CMV antigenemia had to be accompanied by clinical symptoms, signs, and histologic confirmation.[9] Late CMV antigenemia was defined as that occurring after day 100. Ganciclovir or foscarnet was used as pre-emptive therapy to prevent CMV disease. The decision to use pre-emptive therapy was based entirely on a positive antigenemia test (≥3 antigen-positive cells/5×10^4 leukocytes).[7,8] Ganciclovir was administered as an intravenous infusion at the dose of 5 mg/kg/b.i.d. Neutropenic patients (absolute neutrophil count, less than 750/μL) were given foscarnet instead of ganciclovir; the induction dose of foscarnet was 60 mg/kg intravenously every 12 hours, followed by maintenance doses of 90 mg/kg once daily.[10] Treatment was stopped if two consecutive CMV antigenemia assays were negative. Granulocyte colony-stimulating factor was administered when the absolute neutrophil count was <500/μL. Previous reports demonstrated the high sensitivity of the HRP-C7 assay and validated the analyzed cell count and the cut-off we relied on in our study.[7,8]

All UCBT recipients developed CMV antigenemia whereas 44% of the recipients of related matched donor grafts, 70% of the recipients of unrelated matched donor grafts, and 67% of those receiving mismatched related donor transplants did so (Table 2). CMV-associated disease occurred in three patients (4%), gastroenteritis in two and interstitial pneumonia in one. Of these three patients only one patient, who developed interstitial pneumonia after UCBT, died of CMV disease. Forty-one patients (80%) received antiviral therapy; ganciclovir was used in 20 patients, foscarnet in 5, and the combination of both in 16. In the remaining 10 patients, CMV antigenemia remained below the detection level and disappeared without antiviral therapy.

Although our data still require confirmation in a larger

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prospective study, the impact of UCBT on the development of CMV antigenemia might be considered when designing future transplant strategies, at least until more effective methods for prophylaxis of CMV reactivation become available.

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References

1. Ljungman P, Reusser P, de la Camara R, Einsele H, Engelhard D, Ribaud P, et al. Management of CMV infections: recommendations from the infectious diseases working party of the EBMT. Bone Marrow Transplant 2004;33:1075-81.
2. Gluckman E, Rocha V, Boyer-Chammard A, Locatelli F, Arcese W, Pasquini R, et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. N Engl J Med 1997;337:373-81.
3. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. Blood 2003;102: 1915-9.
4. Miyakoshi S, Yuji K, Kami M, Kusumi E, Kishi Y, Kobayashi K, et al. Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematological diseases. Clin Cancer Res 2004;10:3586-92.
5. Harris DT, Schumacher MJ, Locascio J, Besencon FJ, Olson GB, DeLuca D, et al. Phenotypic and functional immaturity of human umbilical cord blood T lymphocytes. Proc Natl Acad Sci USA 1992;89:10006-10.
6. Tomonari A, Iseki T, Ooi J, Takahashi S, Shindo M, Ishii K, et al. Cytomegalovirus infection following unrelated cord blood transplantation for adult patients: a single institute experience in Japan. Br J Haematol 2003;121:304-11.
7. Gondo H, Minematsu T, Harada M, Akashi K, Hayashi S, Taniguchi S, et al. Cytomegalovirus (CMV) antigenaemia for rapid diagnosis and monitoring of CMV-associated disease after bone marrow transplantation. Br J Haematol 1994; 86: 130-7.
8. Takenaka K, Gondo H, Tanimoto K, Nagafuji K, Fujisaki T, Mizuno S, et al. Increased incidence of cytomegalovirus (CMV) infection and CMV-associated disease after allogeneic bone marrow transplantation from unrelated donors. The Fukuoka Bone Marrow Transplantation Group. Bone Marrow Transplant 1997;19:241-8.
9. Zaia JA. Cytomegalovirus infection. In: Blume KG, Forman SJ, Appelbaum F, editors. Thomas' Hematopoietic Cell Transplantation. Third ed. Malden: Blackwell Science; 2004. p. 701-26.
10. Moretti S, Zikos P, Van Lint MT, Tedone E, Occhini D, Gualandi F, et al. Forscarnet vs ganciclovir for cytomegalovirus (CMV) antigenemia after allogeneic hemopoietic stem cell transplantation (HSCT): a randomised study. Bone Marrow Transplant 1998;22:175-80.

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