Annals of Hematology (2019) 98:2613–2615
https://doi.org/10.1007/s00277-019-03827-3

LETTER TO THE EDITOR

Epstein–Barr virus–associated post-transplant lymphoproliferative disorder among long-term survivors of adults after single cord blood transplantation without antithymocyte globulin

Masamichi Isobe[1] · Takaaki Konuma[1] · Seiko Kato[1] · Maki Oiwa-Monna[1] · Yuta Kaito[1] · Satoshi Takahashi[1] · Arinobu Tojo[1]

Received: 24 September 2019 / Accepted: 19 October 2019 / Published online: 29 October 2019

Dear Editor,

Epstein–Barr virus (EBV)–associated post-transplant lymphoproliferative disorder (PTLD) is one of the significant cause of morbidity and mortality among patients after allogeneic hematopoietic cell transplantation (HCT). More than 80% of case usually developed EBV-PTLD within the first year following HCT prior to reconstitution of EBV-reactive adaptive immune response [1, 2]. Cord blood transplantation (CBT) and use of antithymocyte globulin (ATG) was well-known risk factor for development of EBV-PTLD [2, 3]. However, little is known about the long-term incidence of EBV-PTLD after CBT without ATG. Therefore, we retrospectively examined the incidence and outcomes for adults developed EBV-PTLD after CBT without ATG.

Between August 1998 and July 2018, 278 consecutive adult patients who received single-unit CBT as the first allogeneic HCT at our institution were included in this retrospective study. The median age at CBT was 44 years (range, 16 to 69 years). The most common disease type was acute myeloid leukemia (52.5%). The majority of conditioning regimens were total body irradiation 12 Gy-based myeloablative conditioning (87.4%), and the most common graft-versus-host disease (GVHD) prophylaxis was cyclosporine A and methotrexate (86.0%). No patients received ATG, alemtuzumab, or rituximab as a conditioning regimen, GVHD prophylaxis, or prophylactic use for PTLD.

✉ Takaaki Konuma
tkonuma@ims.u-tokyo.ac.jp

[1] Department of Hematology/Oncology, The Institute of Medical Science, The University of Tokyo, 4-6-1, Shirokanedai, Minato-ku, Tokyo 108-8639, Japan

With a median follow-up of 7.2 years (range, 0.1 to 19.2 years) for survivors, seven patients developed EBV-PTLD at a median time of 1131 (range, 73–2930) days (Table 1). The cumulative incidence of EBV-PTLD at 1 year and 7 years were 0.4% (95% confidence interval [CI] 0.0 to1.9%) and 2.4% (95%CI 1.0 to 4.9%), respectively. According to WHO classification, six patients had biopsy-proven EBER–positive PTLD; polymorphic ($n = 1$), monomorphic ($n = 4$), and classical Hodgkin lymphoma ($n = 1$). Serum EBV DNA was detected in 3 among 4 evaluable patients. Only one patient entered complete remission (CR) after withdrawal of immunosuppression, whereas other six patients received conventional chemotherapy based on the histological types of lymphoma. Five of 7 patients achieved CR, whereas the remaining 2 patients died of EBV-PTLD. Among 5 patients achieving CR, 2 patients died of primary disease relapse ($n = 1$) and interatitial pneumonia ($n = 1$).

Previous studies demonstrated that the incidence of EBV-PTLD after CBT ranges between 2 and 4% at a median time of approximately 3 to 6 months, but these studies included the case who used ATG [4–7]. In contrast, our study showed only one patient (0.4%) developed EBV-PTLD within the first year after CBT, whereas 6 patients developed EBV-PTLD over 1 year after CBT. This difference might be dependent on the use of ATG.

Compared with early-onset PTLD, late-onset PTLD is less frequently characterized by EBV positivity after HCT from adult donors [8]. However, our data showed that all six cases developed late-onset PTLD after CBT is associated with EBV. This difference might be in part due to the naïve phenotype of cord blood T cells against EBV and the delayed reconstitution of adaptive immune system after CBT [9]. In conclusion, our data demonstrated that late-onset EBV-PTLD was commonly observed in adults after CBT without ATG.

Table 1 Characteristics of patients who developed EBV-PTLD

Patient no.	1	2	3	4	5	6	7
Age (years)	46	51	47	53	46	37	41
Sex	Male	Male	Female	Female	Male	Male	Male
Primary hematological disease	AML	MM	AML	AML	MDS	ALL	AML
Conditioning regimen	TBI12/Flu/AraC	TBI2/Flu/Mel	TBI12/Flu/AraC	TBI12/AraC/CY	TBI12/AraC/CY	TBI12/AraC/CY	TBI12/AraC/CY
Use of ATG	No	No	No	No	No	No	No
GVHD prophylaxis	CSP+MTX	CSP+MMF	CSP+MTX	CSP+MTX	CSP+MTX	CSP+MTX	CSP+MTX
Cryopreserved TNC dose, *10^7 cells/kg	1.85	2.75	2.57	2.15	2.38	1.82	2.04
Cryopreserved CD34+ dose, *10^5 cells/kg	0.4	0.93	1.11	1.14	1.45	0.42	0.78
HLA mismatch	2	2	2	1	2	2	2
Neutrophil engraftment, days	22	27	32	19	34	21	19
Acute GVHD	I	I	II	II	II	II	II
Chronic GVHD	Limited	Extensive	Limited	Extensive	Extensive	Limited	Extensive
Recipient VCA-IgG at CBT	160	2560	640	< 20	640	1280	40
Recipient VCA-IgM at CBT	< 10	NA	< 10	< 10	< 10	< 10	< 10
Recipient EBNA at CBT	20	20	10	< 10	80	10	10
Recipient CMV serostatus at CBT	+	+	+	+	+	+	+
Time from CBT to PTLD, days	73	699	1397	1113	2930	1359	868
Method of PTLD diagnosis	Duodenum biopsy	Mandibular LN biopsy	Waldyer LN biopsy	BALF, PCR	Inguinal LN biopsy	Small intestine biopsy	Paraaortic LN biopsy
Definiteness of diagnosis	proven	proven	proven	probable	proven	proven	proven
PTLD lineage	B	B	B	B	B	T/NK	B
PTLD pathology	Polymorphic PTLD	Monomorphic PTLD Burkitt type	Monomorphic PTLD Burkitt type	NA	Classical Hodgkin Like - mixed cellular	Monomorphic PTLD T/NK type	Monomorphic PTLD Burkitt type
PTLD stage (Ann-Arbor)	NA	NA	NA	NA	IIIB	IV	IV
PTLD LMP-1 positivity	+	NA	NA	NA	NA	NA	NA
PTLD EBNA-2 positivity	+	NA	NA	NA	NA	NA	NA
PTLD EBER positivity	+	+	+	–	+	+	+
PTLD surface CD20 positivity	NA	+	+	NA	–	–	+
Serum EBV-DNA, copies/ml	–	NA	NA	8*10^4	6*10^2	8*10^2	NA
PTLD Origin - donor vs. recipient	NA	Donor	Donor	NA	NA	NA	NA
Preemptive use of Rituximab	No	No	No	No	No	No	No
Treatment of PTLD	Withdrawal of IS	ChemoTx CODOX-M/IVAC	ChemoTx CALBG-9251	ChemoTx VP-16	ChemoTx ABVD	ChemoTx DeVIC	ChemoTx R-hyper-CVAD-MA
Outcome of PTLD	CR	CR	CR	PR	CR	PR	CR
Overall outcome	Alive	Dead	Alive	Dead	Dead	Dead	Alive
Time from PTLD to death, days	–	1382	–	48	2113	160	–
Cause of death	–	Primary disease relapse	–	PTLD	Interstitial pneumonia	PTLD	–

ALL acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *ATG*, antithymocyte globulin; *BALF*, bronchoalveolar lavage fluid; *CBT*, cord blood transplantation; *CMV*, cytomegalovirus; *CR*, complete remission; *CSP*, cyclosporin A; *CY*, cyclophosphamide; *EBER*, EBV-encoded small RNA; *EBNA*, EB nuclear antigen; *EBV* Epstein-Barr virus; *Flu*, fludarabine; *GVHD*, graft-versus-host disease; *HLA*, human leukocyte antigen; *IS*, immunosuppression; *LMP-1*, Latent membrane protein-1; *LN*, lymph node; *MDS*, myelodysplastic syndrome; *Mel*, melphalan; *MM*, multiple myeloma; *MMF*, mycophenolic acid; *MTX*, methotrexate; *NA*, not assessed; *PR*, partial remission; *PTLD*, post-transplant lymphoproliferative disorder; *TBI*, total body irradiation; *TNC*, total nucleated cells; *VCA*, virus capsid antigen

Acknowledgments The authors thank all of the physicians and staff at the hospital and the cord blood banks in Japan for their help in this study.

Authors' contributions M.I. collected data, and wrote the paper. T.K. conceived the project, designed the research, collected data, analyzed data and wrote the paper. S.K. and M.O. collected data. All the other authors participated in the treatment of the patients, acquired the clinical data, and contributed to writing the paper. All authors approved the final version.

Compliance with ethical standards Written informed consent was acquired from all patients and healthy subjects. The Institutional Review Board of the Institute of Medical Science, University of Tokyo approved this study (30-111-B20190423).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dierickx D, Habermann TM (2018) Post-transplantation lymphoproliferative disorders in adults. N Engl J Med 378:549–562
2. Al Hamed R, Bazarbachi AH, Mohty M (2019) Epstein-Barr virus-related post-transplant lymphoproliferative disease (EBV-PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities. Bone Marrow Transplant. In press
3. Fujimoto A, Hiramoto N, Yamasaki S, Inamoto Y, Uchida N, Maeda T, Mori T, Kanda Y, Kondo T, Shiratori S, Miyakoshi S, Ishiyama K, Ikegame K, Matsuhashi Y, Tanaka J, Ichinohe T, Atsuta Y, Ogata M, Suzuki R (2019) Risk factors and predictive scoring system for post-transplant lymphoproliferative disorder after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 25:1441–1449
4. Barker JN, Martin PL, Coad JE, DeFor T, Trigg ME, Kurtzberg J, Weisdorf DJ, Wagner J (2001) Low incidence of Epstein-Barr virus-associated posttransplantation lymphoproliferative disorders in 272 unrelated-donor umbilical cord blood transplant recipients. Biol Blood Marrow Transplant 7:395–399
5. Brunstein CG, Weisdorf DJ, DeFor T, Barker JN, Tolar J, van Burik JA, Wagner JE (2006) Marked increased risk of Epstein-Barr virus-related complications with the addition of antithymocyte globulin to a nonmyeloablative conditioning prior to unrelated umbilical cord blood transplantation. Blood 108:2874–2880
6. Dumas PY, Ruggeri A, Robin M, Crotta A, Abraham J, Forcade E, Bay JO, Michallet M, Bertrand Y, Socié G, Ionescu I, Gluckman E, Milpied N, Rocha V (2013) Incidence and risk factors of EBV reactivation after unrelated cord blood transplantation: a Eurocord and Société Française de Greffe de Moelle-Therapie Cellulaire collaborative study. Bone Marrow Transplant 48:253–256
7. Sanz J, Arango M, Senent L, Jarque I, Montesinos P, Sempere A, Lorenzo I, Martín G, Moscardó F, Mayordomo E, Salavert M, Cañigral C, Boluda B, Salazar C, López-Hontangas JL, Sanz MA, Sanz GF (2014) EBV-associated post-transplant lymphoproliferative disorder after umbilical cord blood transplantation in adults with hematological diseases. Bone Marrow Transplant 49:397–402
8. Naik S, Riches M, Hari P, Kim S, Chen M, Bachier C, Shaughnessy P, Hill J, Ljungman P, Battiwalla M, Chhabra S, Daly A, Storek J, Ustun C, Diaz MA, Cerny J, Beitinjaneh A, Yared J, Brown V, Page K, Dahi PB, Ganguly S, Seo S, Chao N, Freytes CO, Saad A, Savani BN, Woo Ahn K, Boeckh M, Heslop HE, Lazarus HM, Auletta JJ, Kamble RT (2019) Survival outcomes of allogeneic hematopoietic cell transplants with EBV-positive or EBV-negative post-transplant lymphoproliferative disorder, A CIBMTR study. Transpl Infect Dis 21:e13145
9. Servais S, Hannon M, Peffault de Latour R, Socie G, Beguin Y (2017) Reconstitution of adaptive immunity after umbilical cord blood transplantation: impact on infectious complications. Stem Cell Investig 4:40