ANTICANCER RESEARCH *38*: 6009-6013 (2018)
doi:10.21873/anticanres.12950

Impact of CMV and EBV on Immune Recovery After Allogeneic Hematopoietic Cell Transplantation in Children

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Abstract. *Background/Aim: Immune recovery is a key factor in the management of patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT). This study analyzed the factors contributing to immune reconstitution after allo-HSCT. Patients and Methods: Overall, 65 children with malignant or non-malignant diseases were included in multivariate analyses. Results: The following factors contributed to a faster immune recovery: peripheral blood as a stem cell source and reactivation of CMV infection for $CD3^+$ and $CD4^+$ lymphocyte subpopulations; reactivation of CMV infection for $CD8^+$ subset; donor EBV-IgG^+ and no EBV reactivation for CD19 lymphocytes; recipient age below 10 years and peripheral blood as a stem cell source for NK cells. For CD2 and CD4/CD8 ratio no factor was significant in multivariate analysis. Conclusion: Patients receiving a graft from an EBV-IgG-positive donor and not having early EBV post-transplant viremia show faster recovery of the B-cells, while patients with early CMV-DNA-emia have a better re-establishment of T-cell subsets.*

Hematopoietic stem cell transplantation (HSCT) is an effective therapeutic approach in many malignant and non-malignant diseases including hematological, oncological, immunological and metabolic disorders. The clinical efficacy of HSCT is determined by many factors, including immunological reconstitution of the recipients' immune system. Delayed immune reconstitution might be a common cause of failure of HSCT, mainly due to infectious complications (1), while rapid immune reconstitution is associated with a lower transplantation-related mortality (TRM) and a longer survival after HSCT (2). Many factors might contribute to the efficacy of immune recovery. The objective of this study was the analysis of immune reconstitution by monitoring of lymphocyte subset cell count in children at different time points after allogeneic (allo)-HSCT and analysis of pre- and post-transplant factors affecting the reconstitution, with focus on cytomegalovirus (CMV) and Epstein-Barr virus (EBV) serostatus.

Patients and Methods

Patients. Sixty-five children including 35 boys and 30 girls, who underwent HSCT at a median age of 10 years (range=0.8-18 years), from peripheral blood (PB, n=35) or bone marrow (BM, n=30), from a matched family member (MFD, n=24) or matched unrelated donor (MUD, n=41) for a malignant (acute lymphoblastic leukemia, ALL, n=30; or acute myeloblastic leukemia, AML, n=22) or non-malignant disease (bone marrow failure, BMF, n=13) were included in this study and analyzed for the speed of immune recovery after the transplant and for risk factors influencing lymphocyte reconstitution. Children were eligible for inclusion in this study if they had 10/10 HLA (Human Leukocyte Antigens) MUD or 6/6 matched MFD. In case of unrelated donors, one allelic mismatch was regarded as HLA match. Exclusion criteria were: primary immunodeficiency disorders, subsequent HSCT, relapse or death after HSCT. All children were transplanted between 2010-2014. Informed consents were obtained from the parents. The study was performed according to the institutional guidelines and was approved by the Institutional Review Board.

Transplant procedures. Median infused CD34 cell dose was 6.8×10^6/kg (range=$2.1\text{-}17.7\times10^6$/kg), and median infused CD3 cell dose was 4.1×10^6/kg (range=$1.5\text{-}72.1\times10^6$/kg). Fourteen recipients including all

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Key Words: Hematopoietic cell transplantation, children, immune reconstitution, leukemia, bone marrow failure, CMV, EBV.

BMF patients received a non-myeloablative or reduced intensity conditioning preparative regimen. Anti-thymocyte globulin was used in all MUD transplants and in all BMF patients. Acute (n=15) and chronic (n=7) graft- *vs*. -host disease (GVHD) was assessed according to current standards (3). GVHD prophylaxis consisted of ciclosporin±methotrexate, with addition of methylprednisolone in patients with BMF. All children were prophylactically administered oral antibiotic, acyclovir, fluconazole and cotrimoxazole until the end of the immunosuppressive treatment.

Viral surveillance and infection. CMV and EBV IgG serostatus of donors and recipients were investigated before transplantation (donor: CMV^+, n=30; EBV^+, n=45; recipient: CMV^+, n=36; EBV^+, n=38) (4). After HSCT, all patients underwent weekly blood screening for CMV and EBV reactivation by qPCR at least until day +100. Reactivation of CMV (n=22) or EBV (n=28) was diagnosed when respective DNA-emia was detected. Pre-emptive antiviral therapy was started if the qPCR detected >10,000 copies/ml, both for CMV (n=14/22) and EBV (n=8/28). Preemptive treatment for CMV reactivation included ganciclovir or foscarnet for 2 weeks or until CMV-DNA clearance. Preemptive treatment for EBV reactivation included rituximab weekly (1-4 doses) or until EBV-DNA clearance. Neither CMV end-organ disease nor EBV-related post-transplant lymphoproliferative disorder occurred in the analyzed patients.

Determination of lymphocyte subsets and kinetics of lymphocyte reconstitution. Lymphocyte subpopulations were analyzed in peripheral blood (PB) by flow cytometry at the following eight time points: 1, 3, 6, 9, 12, 15, 18 and 24 months after HSCT. Flow cytometry analysis was performed on FACS Canto II with CellQuest Pro software (Becton Dickinson, BD Biosciences, San Jose, CA, USA) device. Monoclonal antibodies used were the classic T- (anti- CD2, CD3, CD4, CD8), B- (anti-CD19) and natural killer (NK)-cell antigens (anti- CD56 and CD16). At least 10,000 cells were analyzed in each case. The absolute numbers of B-, T-, NK and CD4/CD8 lymphocytes were calculated from total number of PB lymphocytes. Immunological endpoints were determined for their potential clinical significance as defined previously (5) at times where the cell counts were: $CD3^+ > 0.5\times10^9$/l, $CD4^+ > 0.5\times10^9$/l, $CD8^+ > 0.25\times10^9$/l, $CD19^+ > 0.2\times10^9$/l, and $CD3\text{-}CD56^+ > 0.1\times10^9$/l; $CD3^+CD4^+/CD3^+CD8^+$ ratio with cut-off value >1 was also analyzed at each time point.

Statistical analysis. Transplant outcomes, such as overall survival, relapse incidence, transplant-related mortality (TRM), acute and chronic GVHD, were analyzed by the Kaplan–Meier method and compared with the log-rank test. The cumulative incidences of each lymphocyte subset recovery were computed using competing risks events: TRM, infusion of a stem cell rescue and autologous recovery. Baseline parameters were compared between groups using Mann–Whitney or Kruskal–Wallis tests for quantitative variables, and chi-square or Fisher's exact tests for frequencies. Variables studied for their potential impact on lymphocyte recovery were: recipient age, sex, type of transplantation, primary disease, intensity and type of preparative regimen, stem cells source, donor and recipient CMV/EBV pre-transplant serology and post-transplant reactivation. Analysis of factors affecting the rate of immune reconstitution after transplantation was performed using a multivariate logistic regression model (6). Variables relevant to the model were selected based on a threshold p-value <0.1 during univariate analysis. The final models expressed the hazard ratios (HR) and the 95% confidence intervals (95%CI). All the tests were two-sided. Statistical significance was defined as $p<0.05$.

Results

Post-transplant outcomes. The 3-year overall survival was 73% for ALL, 60% for AML and 86% for BMF. Relapse occurred in 27% patients after ALL and in 34.6% after AML ($p=0.5$). TRM was 19.6% in acute leukemia, and 14% in BMF ($p=0.7$). The median time to reach neutrophil recovery was 14 days for acute leukemia and 19 days for BMF ($p<0.001$). Platelet recovery occurred at a median of 18 days and 25 days for acute leukemia and BMF, respectively ($p<0.001$). Acute GVHD occurred in 23.1% patients.

Kinetic of lymphocyte subset recovery. NK cells were the first population that recovered, with a median time to reach $NK>0.1\times10^9$/l of 1 month (range=1-9 months). The next subset of lymphocytes to reconstitute was the B-cell population with a median time to reach $CD19>0.2\times10^9$/l of 6 months (range=1-24 months). The T-cell reconstitution kinetic was slower with a median time to reach $CD2>0.5\times10^9$/l of 9 months, (range=3-24 months), and median time to reach $CD3>0.5\times10^9$/l of 10 months (range=3-24 months). The speed in T-cell reconstitution was associated with a slower CD8 T-cell recovery, as median time to reach $CD8>0.25\times10^9$/l was 11 months (range=3-24 months), and median time to reach $CD4>0.2\times10^9$/l was 12 months (range=3-24 months) ($p<0.001$, for each two parameters separately). The median time to CD4/CD8 ratio >1 was delayed up to 24 months (range=9-24 months). Similar results were observed in analyses performed only for a subgroup of patients with acute leukemia or after exclusion of patients with non-myeloablative conditioning regimen.

Factors affecting incidence of lymphocyte recovery. Using the method of cumulative incidence with competing risks for analysis, the source of stem cells influenced immune reconstitution of all subsets of lymphocytes including CD2, CD3, CD4, CD8, CD19 and NK cells, with univariate analyses identifying slower reconstitution after bone marrow transplantation (Table I). Exclusion of the patients who received a non-myeloablative conditioning regimen or had non-malignant diseases, did not change these results. Patient sex, type of donor, type and intensity of conditioning, type of disease (malignant *vs*. non-malignant) and GVHD had no influence on the recovery of lymphocyte subpopulations.

Univariate analysis. Normalization of NK cells ($CD3\text{-}CD16^+CD56^+$) occurred fast after transplantation. Factors significantly affecting fast reconstitution of NK cells after allo-HSCT included age <10 years and PB as a stem cell source. The speed of immune reconstitution of B cells, characterized by expression of CD19 antigen, was much

Table I. *Univariate analyses of immunologic reconstitution after allo-HSCT.*

Factors	$CD19^+$	$CD2^+$	$CD3^+$	$CD3^+CD4^+$	$CD3^+CD8^+$	CD4/CD8	NK
Age <10 *vs*. ≥10 years	p=0.092	p=0.812	p=0.783	p=0.925	p=0.984	p=0.851	p=0.038
	HR=0.65	HR=0.95	HR=1.21	HR=1.06	HR=1.02	HR=1.13	HR=0.55
PB *vs*. BM	p=0.024	p=0.042	p=0.011	p=0.025	p=0.021	p=0.231	p=0.022
	HR=0.37	HR=0.31	HR=0.42	HR=0.19	HR=0.49	HR=0.63	HR=0.39
Donor	p=0.595	p=0.845	p=0.682	p=0.098	p=0.687	p=0.866	p=0.775
CMV-IgG^+ *vs*. CMV-IgG^-	HR=0.84	HR=0.94	HR=0.86	HR=0.41	HR=1.14	HR=0.92	HR=0.98
Recipient	p=0.678	p=0.411	p=0.526	p=0.814	p=0.724	p=0.981	p=0.712
CMV-IgG^+ *vs*. CMV-IgG^-	HR=0.85	HR=1.19	HR=0.85	HR=1.02	HR=1.13	HR=0.95	HR=1.24
Donor	p=0.082	p=0.571	p=0.200	p=0.539	p=0.348	p=0.743	p=0.414
EBV-IgG^+ *vs*. EBV-IgG^-	HR=0.73	HR=0.97	HR=0.91	HR=0.87	HR=0.95	HR=0.90	HR=0.91
Recipient	p=0.414	p=0.210	p=0.396	p=0.135	p=0.293	p=0.489	p=0.610
EBV-IgG^+ *vs*. EBV-IgG^-	HR=0.91	HR=0.77	HR=0.85	HR=0.74	HR=1.35	HR=0.87	HR=1.16
CMV reactivation *vs*.	p=0.675	p=0.026	p=0.009	p=0.010	p<0.001	p=0.146	p=0.273
no CMV reactivation	HR=0.81	HR=0.55	HR=0.48	HR=0.43	HR=0.24	HR=0.84	HR=0.8
Donor EBV-IgG^+ and	p=0.028	p=0.251	p=0.396	p=0.414	p=0.293	p=0.489	p=0.810
no EBV reactivation *vs*. others	HR=0.35	HR=0.87	HR=0.85	HR=0.98	HR=1.25	HR=0.85	HR=0.98

PB: Peripheral blood; BM: bone marrow; HR: hazard risk.

Table II. *Multivariate analyses for immunologic reconstitution after allo-HSCT.*

Lymphocyte subset recovery	Parameter	HR	95%CI	p-Value
CD3>0.5×10^9/l	CMV reactivation *vs*. no CMV reactivation	0.46	0.32-0.61	0.008
	PB as a stem cell source	0.41	0.30-0.52	0.011
CD4>0.5×10^9/l	CMV reactivation *vs*. no CMV reactivation	0.40	0.28-0.52	0.002
	PB as a stem cell source	0.21	0.14-0.29	0.018
CD8>0.25×10^9/l	CMV reactivation *vs*. no CMV reactivation	0.53	0.39-0.68	0.039
CD19>0.2×10^9/l	Donor EBV-IgG^+ and no EBV reactivation *vs*. others	0.25	0.10-0.39	0.006
NK>0.1×10^9/l	Age <10 years	0.52	0.37-0.67	0.035
	PB as a stem cell source	0.44	0.31-0.56	0.027

PB: Peripheral blood; HR: hazard risk; CI: confidence interval.

faster in patients after the use of PB, however a large variability was observed between analyzed time points of CD19 recovery (p<0.001). Factors affecting fast B-cell reconstitution included: no-TBI conditioning, donor EBV IgG^+ serology and no reactivation of EBV infection.

Reconstitution of T cells, characterized by the expression of CD2 and CD3 antigens, occurred much slower than for B-lineage (p<0.001), and factors affecting fast T-cell restoration included PB as a stem cell source and reactivation of CMV infection. The recovery of $CD3^+CD4^+$ lymphocytes was faster when PB was used as a stem cell source, no-TBI conditioning, donor CMV IgG^+ serology and reactivation of CMV infection. T-cytotoxic $CD3^+CD8^+$ lymphocyte reconstitution was faster when PB was a stem cell source, and after CMV reactivation. The CD4/CD8 index did not achieve normalization within 24 months after allo-HSCT.

CMV and EBV viremia. CMV reactivation within the first 100 days after HSCT contributed in univariate analysis to faster restoration of $CD2^+$, $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$, while positive serological CMV status of donor itself contributed to faster restoration of $CD3^+CD4^+$ only. Positive serological EBV status of donor and no EBV reactivation within the first 100 days after HSCT contributed to faster restoration of $CD19^+$, and also positive serological EBV status of donor itself contributed to faster restoration of $CD19^+$, however significance was not reached (p=0.08).

Multivariate analysis. Factors significantly contributing to faster immune reconstitution are shown in Table II. For CD2 and CD4/CD8 ratio no factor was significant in multivariate analysis.

Discussion

Infection-related mortality is often due to delayed immune recovery after HSCT. This study showed that parameters related to CMV and EBV infection have opposite effects on the speed of the immune reconstitution of lymphocyte subsets in opposite directions: CMV reactivation within the first 100 days after HSCT positively influenced immune recovery of CD3, CD4 and CD8 lymphocyte subsets, while EBV reactivation delayed recovery of CD19 lymphocytes. On the other hand, positive donor CMV and EBV serostatus did not significantly influence the speed of immune recovery of any lymphocyte subset. Also, no impact of preemptive antiviral treatment on lymphocyte recovery both for CMV and EBV viremia (data not shown) was shown, however it was obvious that CD19 recovery was delayed after administration of the anti-CD20 antibody (rituximab) for EBV-reactivation resulting in increased risk of bacterial infections.

CMV, as a latent infection sustained in affected individuals, influences the immune system life-long by changing the profile of T cells in blood (7, 8). Ability to influence T cells might be the basis for the beneficial effect of anti-CMV-IgG positivity of donors' T cells (9). Respective effect of donor and recipient EBV serostatus on post-transplant immune recovery was not observed so far, while EBV viremia had an even negative effect on T-cell recovery after haploidentical transplant (10, 11).

The speed of reconstitution of the immune system is an individual feature of each patient and depends on a large number of variables. The sequence of reconstitution of NK, B and T cells was the same as in other studies (12, 13). Factors that had an influence on fast NK cells recovery in our study were a recipient age below 10 years and PB as a stem cell source. B-cell population usually recovers within 6 months after HSCT (12, 13). The better B cell recovery in EBV^+ patients could be explained by the normal pattern of B-cell stimulation caused by EBV which resides inside donor $CD19^+$ B-cells and is not suppressed by the use of rituximab. Restoration of T-cells is a very complex and lengthier process. Delay in $CD8^+$ recovery could be explained by the higher proportion of immature $CD8^+$ T-cells, which are not stimulated by viruses. CMV specific cytotoxic T-lymphocytes originating from a donor could stimulate lymphocyte reconstitution (14). In our study, children who had a reactivation of CMV infection, had faster $CD4^+$ and $CD8^+$ reconstitution.

Successful immune reconstitution is not only predicted by the presence of T lymphocytes but also by the antigen-specific response. There is probably no complete correlation between the count of each lymphocyte subset and the presence or absence of an antigen-specific response, but naive T lymphocytes are able to contribute to the generation of antigen-specific T lymphocyte immunity early after transplantation. In patients who are positive for anti-CMV-IgG antibodies, the immune system is more efficient shortly after transplantation. Higher levels of $CD4^+CD25^+$ lymphocytes increase the chances of survival (7). Anti-CMV-IgG positivity is closely correlated with the presence of a cellular response in the same individual and reflects primary CMV infection and the presence of the virus in a latent form (15, 16). Reactivation events boost the immune response, promoting the effectiveness of specific surveillance (8). Lugthart *et al.* showed also that CMV reactivation early after HSCT in children leaves a specific and dynamic imprint on the size and composition of the $CD8^+$ cell pool without compromising the reconstitution of $CD8^+$ and $CD4^+$ naive and central memory T cells pivotal in the response to antigens (17).

In conclusion, our data suggest that patients receiving graft from EBV-IgG-positive donor and not having early EBV post-transplant viremia show faster recovery of of B-cells, while patients with early CMV-DNA-emia have a better reconstitution of T-cell subsets.

References

1 Kalwak K, Gorczynska E, Toporski J, Turkiewicz D, Slociak M, Ussowicz M, Latos-Grazynska E, Krol M, Boguslawska-Jaworska J and Chybicka A: Immune reconstitution after haematopoietic cell transplantation in children: immunophenotype analysis with regard to factors affecting the speed of recovery. Br J Haematol *118*: 74-89, 2002.

2 Koenig M, Huenecke S, Salzmann-Manrique E, Esser R, Quaritsch R, Steinhilber D, Radeke HH, Martin H, Bader P, Klingebiel T, Schwabe D, Schneider G, Lehrnbecher T, Orth A and Koehl U: Multivariate analyses of immune reconstitution in children after allo-SCT: risk-estimation based on age-matched leukocyte sub-populations. Bone Marrow Transplant *45*: 613-621, 2010.

3 Nassereddine S, Rafei H, Elbahesh E and Tabbara I: Acute graft versus host disease: a comprehensive review. Anticancer Res *37*: 1547-1555, 2017.

4 Dziedzic M, Sadowska-Krawczenko I and Styczynski J: Risk factors for cytomegalovirus infection after allogeneic hematopoietic cell transplantation in malignancies: proposal for classification. Anticancer Res *37*: 6551-6556, 2017.

5 Renard C, Barlogis V, Mialou V, Galambrun C, Bernoux D, Goutagny MP, Glasman L, Loundou AD, Poitevin-Later F, Dignat-George F, Dubois V, Picard C, Chabannon C, Bertrand Y and Michel G: Lymphocyte subset reconstitution after unrelated cord blood or bone marrow transplantation in children. Br J Haematol *152*: 322-330, 2011.

6 Illiaquer M, Imbert-Marcille BM, Guillaume T, Planche L, Rimbert M, Bressollette-Bodin C, Le Bourgeois A, Peterlin P, Garnier A, Le Houerou C, Moreau P, Mohty M and Chevallier P: Impact of stem cell graft on early viral infections and immune reconstitution after allogeneic transplantation in adults. J Clin Virol *93*: 30-36, 2017.

7 Herndler-Brandstetter D, Landgraf K, Tzankov A, Jenewein B, Brunauer R, Laschober GT, Parson W, Kloss F, Gassner R, Lepperdinger G and Grubeck-Loebenstein B: The impact of aging on memory T cell phenotype and function in the human bone marrow. J Leukoc Biol *91*: 197-205, 2012.

8 Jaskula E, Dlubek D, Tarnowska A, Lange J, Mordak-Domagala M, Suchnicki K, Sedzimirska M, Borowik A, Mizia S and Lange A: Anti-CMV-IgG positivity of donors is beneficial for alloHSCT recipients with respect to the better short-term immunological recovery and high level of $CD4^{+}CD25^{high}$ lymphocytes. Viruses *7*: 1391-1408, 2015.

9 Ljungman P, Brand R, Hoek J, de la Camara R, Cordonnier C, Einsele H, Styczynski J, Ward KN, Cesaro S, Infectious Diseases Working Party of the European Group for B and Marrow T: Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European group for blood and marrow transplantation. Clin Infect Dis *59*: 473-481, 2014.

10 Bian Z, Liu J, Xu LP, Chang YJ, Wang Y, Zhang XH and Huang XJ: Association of Epstein-Barr virus reactivation with the recovery of CD4/CD8 double-negative T lymphocytes after haploidentical hematopoietic stem cell transplantation. Bone Marrow Transplant *52*: 264-269, 2017.

11 Liu J, Bian Z, Wang X, Xu LP, Fu Q, Wang C, Chang YJ, Wang Y, Zhang XH, Jiang Z and Huang XJ: Inverse correlation of Vdelta2(+) T-cell recovery with EBV reactivation after haematopoietic stem cell transplantation. Br J Haematol *180*: 276-285, 2018.

12 Moretta A, Maccario R, Fagioli F, Giraldi E, Busca A, Montagna D, Miniero R, Comoli P, Giorgiani G, Zecca M, Pagani S and Locatelli F: Analysis of immune reconstitution in children undergoing cord blood transplantation. Exp Hematol *29*: 371-379, 2001.

13 Niehues T, Rocha V, Filipovich AH, Chan KW, Porcher R, Michel G, Ortega JJ, Wernet P, Gobel U, Gluckman E and Locatelli F: Factors affecting lymphocyte subset reconstitution after either related or unrelated cord blood transplantation in children - a Eurocord analysis. Br J Haematol *114*: 42-48, 2001.

14 Hanley PJ, Cruz CR, Savoldo B, Leen AM, Stanojevic M, Khalil M, Decker W, Molldrem JJ, Liu H, Gee AP, Rooney CM, Heslop HE, Dotti G, Brenner MK, Shpall EJ and Bollard CM: Functionally active virus-specific T cells that target CMV, adenovirus, and EBV can be expanded from naive T-cell populations in cord blood and will target a range of viral epitopes. Blood *114*: 1958-1967, 2009.

15 Alcami A and Koszinowski UH: Viral mechanisms of immune evasion. Trends Microbiol 8: 410-418, 2000.

16 Sester M, Gartner BC, Sester U, Girndt M, Mueller-Lantzsch N and Kohler H: Is the cytomegalovirus serologic status always accurate? A comparative analysis of humoral and cellular immunity. Transplantation *76*: 1229-1230, 2003.

17 Lugthart G, van Ostaijen-Ten Dam MM, Jol-van der Zijde CM, van Holten TC, Kester MG, Heemskerk MH, Bredius RG, van Tol MJ and Lankester AC: Early cytomegalovirus reactivation leaves a specific and dynamic imprint on the reconstituting T cell compartment long-term after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant *20*: 655-661, 2014.

Received July 29, 2018
Revised August 21, 2018
Accepted August 24, 2018