Cord Blood Forum

Annotated Bibliography

XIII. Immune Reconstitution

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1. **Immunobiology of allogeneic hematopoietic stem cell transplantation**. Welniak LA, Blazar BR, Murphy WJ. Annu Rev Immunol. 2007;25:139-170. Abstract

   This is an extensive and very informative review that discusses a wide variety of topics. Included are (1) Clinical considerations of allogeneic HSCT, (2) Conditioning, graft manipulation, and post-transplant protocols for allogeneic HSCT, (3) Histocompatibility antigen testing in HSCT, (4) Preclinical models for the study of allogeneic HSCT, (5) Barriers in allogeneic HSCT (graft rejection and immune reconstitution) and (6) a detailed discussion of GVHD and GVT including a review of the pathophysiology of GVHD, presentation of alloantigens, T cell subsets and GVHD and GVT, T cell costimulation and GVHD, T cell trafficking and GVHD, effector functions of T cells and their role in GVHD, molecular targeting of GVHD and the role of other lymphocytic subpopulations in allogeneic HSCT (T regulatory cells and NK cells). **There are 235 reference citations**.

   The authors emphasize that much of the immunobiology of allogeneic HSCT has been gleaned from preclinical models and correlation with clinical observations. They suggest that preclinical allogeneic HSCT models will continue to be invaluable in increasing our understanding of the immunobiology of HSCT and its application.

   This is a valuable article for those wishing a review of any of the above aspects of the immunobiology of HSCT.

2. **Immune reconstitution after unrelated cord blood transplantation**. A Review. Szabolcs P, Niedzwiecki D. Cytotherapy. 2007;9:111-122. Abstract

   This review provides an overview of what has been learned over the past decade regarding the reconstitution of adaptive immunity following UCBT, and illustrates this with some of the authors' own findings in the pediatric setting.

   Despite the considerable progress over the past decade in supportive care after HCT, opportunistic infections (OI) remain a major cause of morbidity and mortality, largely because of the delayed or perturbed immune reconstitution after HCT. Infection-related mortality is the primary cause of death after umbilical cord blood transplantation (UCBT) with most deaths occurring in the first 3-6 months post transplant.

   For several months, until recovery of the thymus is restored to support de novo T cell generation, protective antiviral immunity depends on the activity of post-thymic T cells infused within the cord blood (CB) grafts. However, almost all CB T cells are antigen inexperienced (naïve) lymphocytes that have been functionally altered by placental factors to protect pregnancy. CB T cells need to undergo in vivo priming, Th1/Tc1 maturation, and peripheral expansion before they can afford immunologic protection.

   Remarkable immunophenotypic changes are notable already in the first 2-3 weeks post-UCBT. These changes result from apparent 'homeostatic' peripheral T cell expansion in the lymphopenic environment. While one can identify patient- and graft-specific predictive factors, **the concordant emergence of T cell subsets displaying the phenotype of Th1/Tc1 cytotoxic effector cells can be statistically linked to those UCBT recipients who will subsequently develop viral and other opportunistic infections**. Antigen presenting dendritic cell reconstitution may also reflect alterations in immunocompetence due to OI and/or GVHD.

   Collectively, these early phenotypic alterations demonstrate significant advances in the adaptive immune system toward the development of effective anti-viral immunity, despite ongoing pharmacologic immunosuppression to prevent GVHD. There are also significant patient- and graft-specific risk factors for acquiring or dying from opportunistic infections, most notably older age, positive CMV serology, >1 HLA mismatch and lower graft cell dose.

   There is a great need to learn more about the biology of immune recovery after UCBT. However, there is also realistic hope that novel immunotherapy strategies could enhance immune competence to reduce infectious morbidity and mortality after UCBT.

3. **Immune reconstitution in children after unrelated cord blood transplantation**. Szabolcs P, Niedzwiecki D. Biol Blood and Marrow Transplant 2008;14 (Suppl 1):66-72.

   Infection-related mortality is the primary or secondary cause of death (with or without another major cause such as GVHD) in 50% of deaths after UCBT, with the majority of them occurring in the first 100 days. Two studies have demonstrated increase occurrence of severe infections during the first 100 days after UCBT than in BMT/PBSC groups. However, subsequently there was a trend toward less serious infection in the UCBT group suggesting that the immune deficit that seems to be so heightened in the immediate post-UCBT period is followed by significant improvements of immunity.

   After immunoablation the innate immune system appears to recover rapidly, within weeks after HCT, but the recovery of functional B and T lymphocytes (adaptive immunity) is far more difficult to achieve. The first wave of T cells emerging in the lymphopenic host consists of peripherally expanding T lymphocytes representing the thymic-independent pathway. Several weeks/months later a second wave of T cells emerge developing from donor-derived common lymphocyte progenitors as a result of de novo thymopoiesis. By 2 years after HCT higher TCR diversity may be attained in CB recipients than in recipients of BMT, indicating the existence of an efficient thymic-dependent pathway.

   The authors' studies have demonstrated several graft- and patient-specific variables that are also identified as significant factors when the laboratory measurements of dendritic cell (DC) and T cell reconstitution were analyzed. In the pediatric cohort, 6-month death because of OI can be predicted by the following risk factors: older age, positive CMV serology, >1 HLA mismatch, malignancy without TBI, and lower graft cell dose (total, $CD34^+$ and $CD3^+$). In contrast, sex, race, and TBI alone do not predict 6-month death because of OI.

Additional studies have indicated that on the immediate posttransplant lymphopenic period extensive T cell proliferation via peripheral expansion leads to major immunophenotypic alterations accompanied by a gradual loss of the original naïve phenotype. In parallel, new T cells subsets emerge displaying a phenotype associated with antigenic stimulation. The authors hypothesize that in patients who will develop OI, even clinically undetectable levels of virus could induce phenotypic acquisition of Th12/Tc1 cytotoxic effector profile.

There is realistic hope that clinical translation of new immunotherapy strategies could enhance immune competence after UCBT either by having an impact on the thymic-independent early period of by fostering thymic recovery.

4. **Delayed immune reconstitution after cord blood transplantation is characterized by impaired thymopoiesis and late memory T-cell skewing**. Komanduri KV, St John LS, de Lima M, McMannis J, Rosinski S, McNiece I, Bryan SG, Kaur I, Martin S, Wieder ED, Worth L, Cooper LJ, Petropoulos D, Molldrem JJ, Champlin RE, Shpall EJ. Blood. 2007;110:4543-4551. Full Text

   In the introduction to this article the authors underscore the importance of cord blood transplants, especially for recipients in historically underrepresented minority groups, for whom the prospect of locating MUD registry donor remains relatively diminished. The authors point out that at the author's institution, more than twice the proportion of CB transplant recipients are minorities relative to MUD marrow or PBSC recipients historically undergoing transplantations.

   This is a report of the results of a single-center prospective study of T-cell immune recovery after cord blood transplantation (CBT) in a predominantly adult population. The primary findings include the following: (1) Prolonged T lymphopenia and compensatory expansion of B and natural killer (NK) cells was evident; (2) CB transplant recipients had impaired functional recovery, although posttransplantation de novo T-cell responses to cytomegalovirus (CMV) was observed in a subset of patients; (3) Thymopoietic failure characterized post-CBT immune reconstitution, in marked contrast to results in other transplant recipients; and (4) Thymopoietic failure was associated with late memory T-cell skewing.

   These data suggest that efforts to improve outcomes in adult CB transplant recipients should be aimed at optimizing T-cell immune recovery. Strategies that improve the engraftment of lymphoid precursors, protect the thymus during pretransplant conditioning, and/or augment the recovery of thymopoiesis may improve outcomes after CBT.

5. **Immune reconstitution after allogeneic stem cell transplantation with reduced-intensity conditioning regimens.** Jiménez M, Ercilla G, Martínez C. Leukemia. 2007;21:1628-37. Abstract

   This article provides an excellent review of the factors that make difficult the comparison between reduced-intensity stem cell transplants (RIC-SCT) and myeloablative conditioning stem cell transplants (MAC-SCT) in regard to immune reconstitution. A theoretical advantage of RIC-SCT is that it might lend to better immune reconstitution after transplantation due to less damage of the thymus, allowing regeneration of naive T cells derived from prethymic donor stem cells, and due to the proliferation of immunologically competent host T cells that survive the conditioning regimen. However, published studies have shown contradictory findings. Several factors contribute to the difficulty of the comparison. So far, no randomized studies are available since RIC-SCT has generally been reserved for elderly patients, patients that have received a previous autologous SCT, or patients with organ dysfunction who are not candidates for MAC regimens. Further, the myelosuppressive and immunosuppressive capacities of diverse RIC regimens vary depending on the protocol and, therefore, their impact on immune reconstitution after transplantation may be different.

   The authors first review T-cell reconstitution (methods of analysis of T-cell reconstitution after SCT, thymic-independent T-cell reconstitution, and thymopoiesis after RTIC-SCT), and then review B and NK cell reconstitution, and dendritic cell reconstitution. They then review factors affecting immune reconstitution after RIC-SCT including GVHD, patient's age and chimerism.

   The authors conclude by stating that immune reconstitution after RIC-SCT remains a field for debate. The current spectrum of RIC protocols, which vary considerably in myeloablative and immunosuppressive potential, and the absence of randomized studies comparing RIC-SCT to MAC-SCT make it difficult to draw accurate conclusions. Published studies so far suggest that the use of RIC regimens in allogeneic SCT results in significant quantitative and/or qualitative differences in immune reconstitution in comprison with conventional MAC-SCT. Several authors have reported faster recovery of total lymphocytes, memory and naïve CD34+ lymphocytes, and TRECs levels at least during the first months after RIC-SCT. More rapid reconstitution of T-cell repertoire complexity has also been observed. A combination of thymus function preservation and peripheral expansion of donor and residual host mature lymphocytes could explain these results. Despite these differences, infectious complications and relapse remain major causes of morbidity and mortality after RIC-SCT.

6. **Antigen-specific T-lymphocyte function after cord blood transplantation**. Cohen G, Carter SL, Weinberg KI, Masinsin B, Guinan E, Kurtzberg J, Wagner JE, Kernan NA, Parkman R. Biol Blood Marrow Transplant. 2006;12:1335-42. Abstract

   The T lymphocytes present in the HSC inoculum are composed of both naïve and antigen-specific T lymphocytes. However, it has not been possible to determine the relative contributions of donor-derived antigen-specific and naïve T lymphocytes to antigen-specific immune reconstitution after HLSCT because of the confounding effects of donor-derived antigen-specific T lymphocytes present in most hematopoietic stem cell (HSC) products. Because **umbilical cord blood contains only naïve T lymphocytes**, unrelated cord blood transplantation (UCBT) represents a unique clinical opportunity to determine the contributions of naïve T lymphocytes to post-transplantation antigen-specific immunity without the impact of donor-derived antigen-specific T lymphocytes.

   Antigen-specific T lymphocytes were detected early after UCBT (herpes simplex virus on day 29; cytomegalovirus on day 44; varicella zoster virus on day 94). Overall, 66 of 153 UCBT recipients developed antigen-specific T lymphocytes to 1 or more herpes viruses during the evaluation period. The likelihood of developing antigen-specific T lymphocyte function was not associated with immunophenotypic T lymphocyte reconstitution, transplant cell dose, primary disease, or acute and chronic graft-versus-host disease.

   These results indicate that naïve T lymphocytes present in the HSC inoculum can contribute to the generation of antigen-specific T-lymphocyte immunity early after transplantation.

7. **Successful immune reconstitution decreases leukemic relapse and improves survival in recipients of unrelated cord blood transplantation**. Parkman R, Cohen G, Carter SL, Weinberg KI, Masinsin B, Guinan E, Kurtzberg J, Wagner JE, Kernan NA. Biol Blood Marrow Transplant. 2006; 12:919-927. Abstract

   After HSCT, antileukemic immune responses are believed to eliminate residual leukemia cells and decrease the likelihood of relapse. If adequate antigen-specific immune function is present the new donor-derived immune system has the potential to decrease leukemic relapse and infectious deaths. **Because of the confounding effects of GVHD, it has been difficult to determine the effect of successful immune reconstitution on leukemic relapse and relapse-free survival. Patients who undergo unrelated cord blood transplantation have a decreased incidence of GVHD compared with patients who received unrelated BM or PBSC transplants**. Therefore, the clinical effect of the development of antigen-specific T-lymphocyte immunity on leukemic relapse and relapse-free survival was evaluated after umbilical cord blood transplantation.

Pediatric recipients of unrelated cord blood transplants who underwent transplantation for acute leukemia were sequentially evaluated for their development of antigen-specific T-lymphocyte immunity to herpes viruses. The clinical effect of positive antigen-specific response on relapse-free survival was determined.

The presence of an antigen-specific response resulted in a relapse-free survival advantage (P=0.0001), which was primarily due to a decrease in leukemic relapse (P=0.003). Proportional hazards modeling for time and relapse and time to relapse or death defined 3 variables that were strongly associated with a poor outcome: female gender, poor remission status before transplantation, and negative antigen-specific T-lymphocyte proliferation. Notably neither acute nor chronic GVHD had any effect on the incidence of leukemic relapse.

Further clinical research should be directed at prospective studies of the effect of the development of antigen-specific immune function after neoantigen immunization and improving he immune reconstitution of HSC transplant recipients with documented defects in antigen-specific T-lymphocyte function. **The successful immune reconstitution of such recipients may result in a decreased incidence of leukemic relapse and death, resulting in improved survival of HSC transplant recipients**.

8. **Analysis of engraftment, graft-versus-host disease, and immune recovery following unrelated donor cord blood transplantation**. Thomson BG, Robertson KA, Gowan D, Heilman D, Broxmeyer HE, Emanuel D et al. Blood 2000; 96:2703-2711. Full Text

Thirty cord blood transplant procedures were performed for both malignant and nonmalignant diseases in 27 children. Patients received either HLA-matched (n=3) or 1 or 2-antigen mismatched (n= 27) cord blood transplants following 1 of 2 standardized preparative and GVHD regimens. CD4, CD19 and NK cell recovery was achieved at a median of 12, 6, and 2 months, respectively. CD8 recovery was delayed at a median of 9 months. Normal mitogen response was achieved at 6 to 9 months. The authors concluded that in this series of 30 children, although CD8 recovery was delayed, the pattern of immune reconstitution with cord blood units is similar to that reported for other stem cell sources.

9. **Factors affecting lymphocyte subset reconstitution after either related or unrelated cord blood transplantation in children -- a Eurocord analysis**. Niehues T, Rocha V, Filipovich AH, Chan KW, Porcher R, Michel G et al. Br J Haematol 2001; 114:42-48. Abstract

Immune recovery after cord blood transplantation is of concern owing to the low number of lymphocytes transferred with the graft and their immaturity. Risk factors influencing lymphocyte subset reconstitution related to disease, patient, donor and transplant were studied in 63 children (< 16 years), given either related (n = 14) or unrelated (n = 49) cord blood transplants for malignant (n = 33) or non-malignant diseases (n = 30). Only children with sustained myeloid engraftment were analysed. Absolute numbers of T (CD3(+), CD4(+), CD8(+)), B and natural killer (NK) cells were reported 2--3, 6, 9, 12 and 12--24 months after CBT. Median patient age was 4.0 years (0--15) and median follow-up was 23 months (1.7--61.0). Twenty-six patients received human leucocyte antigen (HLA)-matched CBT and 37 received HLA-mismatched CBT. The median number of nucleated cells (NCs) collected/recipient weight was 6.1 x 10^7/kg. In this selected population, the estimate 2 year survival was 85%. Lymphocyte reconstitution (defined as the median time to reach the normal value of age-matched healthy children) was 3, 6 and 8 months for NK, B and CD8(+) cells, while it was 11.7 months for both CD3(+) and CD4(+) lymphocytes. In the multivariate analysis, factors favoring T-cell recovery were: related donor (P = 0.002); higher NCs/kg (P = 0.005) and recipient cytomegalovirus (CMV)-positive serology (P = 0.04). Presence of acute graft-versus-host disease (GVHD) delayed T-cell recovery (P = 0.04). *To summarize, in children with sustained myeloid engraftment the concern that lymphocyte recovery after CBT could be delayed does not appear to be substantiated by our results*.

10. **T-Cell recovery in adults and children following umbilical cord blood transplantation**. Klein AK, Patel DD, Gooding ME, Sempowski GD, Chen BJ, Liu C et al. Biol Blood Marrow Transplant 2001; 7:454-466. Abstract

The authors measured quantitative and qualitative immunologic reconstitution and T cell-receptor excision circle (sjTREC) levels in adult and pediatric recipients of umbilical cord blood transplants. sjTRECs were detected at normal levels in all children, starting 12 months after transplantation. sjTRECs were not detected until 18 months after transplantation in adults, and then only at a 3-fold lower level than expected for age. T-cell repertoires were skewed in adults and children at 12 to 18 months after transplantation but recovered to near-normal diversity at 2 to 3 years post-UCBT. T-cell repertoires appeared more diverse earlier in children (at 1 to 2 years post-UCBT) than in adults (at 3 to 4 years post-UCBT). The delay in central T-cell recovery in adults relative to children may be due to differences in thymic function resulting from age-related atrophy, graft-versus-host disease, or the pharmacologic effects of prophylaxis and treatment of graft-versus-host disease.

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11. **A broad T-cell repertoire diversity and an efficient thymic function indicate a favorable long-term immune reconstitution after cord blood stem cell transplantation.** Talvensaari K, Clave E, Douay C, Rabian C, Garderet L, Busson M, Garnier F, Douek D, Gluckman E, Charron D, Toubert A. Blood. 2002;99:1458-1464. Full Text

This study was designed to evaluate T-cell reconstitution using combined approaches of phenotyping, analysis of alphabeta T-cell receptor (TCR) diversity, and assessment of ex vivo thymic function by measuring TCR rearrangement excision circles (TRECs). Ten patients who underwent CB transplantation for high-risk hematologic disorders were compared to a reference group of 19 age- and GVHD-matched patients who underwent transplantation with non-T cell-depleted bone marrow from an HLA-identical sibling donor. TREC values correlated with the relative number of naive T cells and with TCR repertoire polyclonality. During the first year after transplantation, TCR repertoires were highly abnormal and TREC values low in both groups. Notably, 2 years after transplantation onward TREC values as well as TCR diversity were higher in CB recipients than in recipients of bone marrow transplants. The authors state that their data indicate an efficient thymic regeneration pathway from CB lymphoid progenitors despite the low number of cells infused compared to bone marrow, arguing for a complete clinical immune recovery after CB transplantation.

12. **T lymphocytes of recipient origin may contribute to the recovery of specific immune response toward viruses and fungi in children undergoing cord blood transplantation**. Montagna D, Locatelli F, Moretta A, Lisini D, Previdere C, Grignani P, DeStefano P, Giorgiani G, Montini E, Pagani S, Comoli P, Maccario R. Blood. 2004;103:4322-9. Abstract

Cord blood lymphocytes are naïve cells, with low T-cell-mediated cytotoxic capacity and, in vitro, markedly reduced responsiveness to allogeneic stimuli in secondary mixed lymphocyte reaction. There are concerns that patients undergoing allogeneic cord blood transplantation (CBT) may not be able to recover an effective immune capacity early after transplantation. The aims of the study were to evaluate the ability of recipients of cord blood transplants to develop an in vitro immune response toward 2 widespread pathogens (CMV and *Candida Albicans*), both early and late after transplantation and to define the origin, either donor or patient, of T cells contributing to the immune response. The studies were performed in children given cord blood transplants from either an HLA-identical sibling or an unrelated donor. Proliferative capacity and frequency of antigen-specific T cells were evaluated; antigen-specific CD4(+) T-cell clones were also generated and characterized for T-cell receptor repertoire diversity, cytokine phenotype, and their origin (either from donor or patient). Results indicated that the majority of recipients developed a specific response to viral or fungal antigens early after transplantation. Antigen-specific T-cell clones of both donor and recipient origin contributed to the immune reconstitution. Antigen-specific T lymphocytes of recipient origin were detected in patients receiving a transplant from a relative, after a chemotherapy-based conditioning regimen, and who did not have GVHD. These studies document, at a clonal level, that after CBT recovery of either polyclonal or pauciclonal T-cell response toward widespread pathogens is prompt, with some patients benefiting from a contribution of recipient-derived cells. The authors further stated that their data support previously reported results indicating a post-CBT recovery of T-lymphocyte number and a response to polyclonal activators at least comparable to that observed in BMT recipients and characterized by a fully reconstituted TCR repertoire. However, all of the patients studied were children, most received a CBT from an HLA-identical sibling, and none developed GVHD; these factors may contribute to the prompt recovery of T-cell-mediated antigen-specific immune responses.

13. **Immune restoration following hematopoietic stem cell transplantation: an evolving target**. Auletta JJ, Lazarus HM. Bone Marrow Transplant. 2005;35: 835-57. Abstract

The **goals of the authors of this review** were to (1) review immune effector cells and their function as they relate to HSCT, (2) review immune reconstitution across transplant regimens and stem cell sources; and (3) offer potential considerations for modulating or restoring immune responses during HSCT. They provide a detailed review (22 pages) including 5 tables and a figure.

In regard to stem cell source used during HSCT, the authors indicate that rates of life-threatening opportunistic infection were similar between pediatric UCB and age-/GVHD-matched sibling-donor BM recipients. UCB patients had higher naïve /CD4+ T cells, TREC levels, and TCR diversity after 2 years post-transplant despite receiving lower CD34+ cells. In contrast, when compared to HLA-matched unrelated donor allogeneic transplantation in adults, UCB recipients had higher infection rates during the first 50 days post-transplant and greater overall bacterial infections attributed to delayed PMN cell and lymphocyte recovery.

This paper reviews current understanding for immune restoration following HSCT and the novel ways in which to restore immune function and decrease transplant-related toxicity in the transplant recipient. The authors provide a detailed discussion of immunotherapy, including cellular factors as targets for immunotherapy, expansion of beneficial cell types, depletion of harmful effector cells, soluble factors and their targets, hematopoiesis and stem cell mobilization, activation or augmentation of effector cell function, inactivation or attenuation of effector cell function, effector cell localization and migration, tissue protection and restoration and immunomodulation, as well as a discussion of future directions.

14. **Immune reconstitution following haematopoietic stem cell transplantation**. Peggs KS, Mackinnon S. Br J Haematol. 2004;124:407-20. Abstract

The authors provide a comprehensive review of immune reconstitution following hematopoietic stem cell transplantation. The emphasis is on the extensive and complex laboratory evaluations that are available to research laboratories rather than on clinical data. The current state-of-the-art techniques for monitoring immune reconstitution are reviewed in depth. Details are provided regarding T-cell reconstitution including thymic-independent expansions and thymic-dependent reconstitution. Further information is provided regarding the influence of GVHD and chimerism status, reconstitution of antigen-specific T cell responses, B-cell reconstitution, NK cell reconstitution and the effect of stem cell source. The authors conclude that the tools are now available to more carefully dissect the interrelated elements of immune reconstitution, and to monitor the impact of attempts to enhance immune recovery. Although cytokine-based therapies and unselected DLI offer some potential, they point out that part of the immune defect posttransplantation is intentionally induced and maintained in order to limit the risk of development of GVHD. Increased knowledge about immune reconstitution may help to harness the immunological potential of allogeneic transplantation by guiding the need for, and appropriate timing of, post-transplantation interventions.

15. **Long-term immune recovery of patients undergoing allogeneic stem cell transplantation: a comparison with their respective sibling donors**. Sanchez-Guijo FM, Sanchez-Abarca LI, Bueno C, Villaron E, Lopez-Holgado N, Vazquez L, Lopez-Fidalgo J, Perez-Simon JA, Caballero MD, del Canizo MC, Orfao A, San Miguel JF. Biol Blood Marrow Transplant. 2005;11:354-61.
Abstract

The major goal of this study was to evaluate the status of the immune system at least 1 year after transplantation in a series of 38 patients who had received an HLA-identical sibling allo-SCT and to compare it with that of their respective related donors. The study focused on the numeric and functional analysis not only of the different subsets of peripheral blood (PB) lymphocytes, but also of circulating dendritic cell (DC) subpopulations. The results were evaluated simultaneously in a patient/donor paired study performed only after complete bone marrow chimerism and normal PB cell counts were shown in all recipients. An additional goal of this study was to analyze the status of the immune system in a group of patients receiving a reduced-intensity conditioning (RIC) regimen as compared with those undergoing conventional myeloablative transplantations.

Results indicated the existence of several numeric and functional differences in distinct cellular compartments of the immune system of patients as compared with their respective donors. The most relevant numeric differences were related to the distribution of the distinct subsets of PB DCs ($CD16^+$ DCs were increased, whereas myeloid and plasmacytoid DC subsets were decreased in the patient group). This was associated with an increased number of B cells, an inverted CD4/CD8 T-cell ratio, and a decrease in $CD4^+/CD8^+$ double-positive T cells in the patient group. In addition, a predominance of a T-helper 1 pattern of cytokine production (interferon ? and tumor necrosis factor ?) with decreased secretion of T-helper 2-associated cytokines (interleukin 5 and interleukin 10) was also observed at the single-cell level. No significant differences were found in any of the parameters analyzed between patients receiving reduced-intensity conditioning regimens and those undergoing myeloablative transplantations.

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