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Humoral Immune Reconstitution Kinetics after Allogeneic Hematopoietic Stem Cell Transplantation in Children: A Maturation Block of IgM Memory B Cells May Lead to Impaired Antibody Immune Reconstitution

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A B S T R A C T

Although T cell immune reconstitution after allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been well studied, long-term B cell immune reconstitution remains less characterized. We evaluated humoral immune reconstitution among 71 pediatric allo-HSCT recipients. Although tetanus toxoid antibody levels were normal at 1 year after allo-HSCT, antipolysaccharide carbohydrate antibodies remained persistently low for up to 5 years. While naive B cell counts normalized by 6 months, IgM memory B cell deficiency persisted for up to 2 years ($P = .01$); switched memory B cell deficiency normalized by 1 year after allo-HSCT. $CD4^+$ T cell immune reconstitution correlated with that of switched memory B cells as early as 6 months after allo-HSCT ($r = .55$, $P = .002$) but did not correlate with IgM memory B cells at any time point after allo-HSCT. Taken together, this suggests that allo-HSCT recipients have impaired antibody immune reconstitution, mainly due to IgM memory B cell maturation block, compared with more prompt T cell–dependent switched memory cell immune reconstitution. We further explored other factors that might affect humoral immune reconstitution. The use of total body irradiation was associated with lower naive B cells counts at 6 months after HSCT ($P = .04$) and lower IgM ($P = .008$) and switched ($P = .003$) memory B cells up to 2 years. Allo-HSCT recipients with extensive chronic graft-versus-host disease had lower IgM memory B cell counts ($P = .03$) up to 2 years after allo-HSCT. The use of cord blood was associated with better naive ($P = .01$), IgM ($P = .0005$), and switched memory ($P = .006$) B cells immune reconstitution. These findings may inform future prophylaxis and treatment strategies regarding risk of overwhelming infection, graft-versus-host disease, and post-allogeneic HSCT revaccination.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative therapy for a wide range of malignant and nonmalignant diseases. However, delays in immune reconstitution after allo-HSCT are associated with infectious morbidity and mortality and graft-versus-host-disease (GVHD), and they represent significant barriers to successful outcomes [1-3]. The kinetics associated with long-term B cell immune reconstitution after allo-HSCT remain poorly characterized. Hematopoietic stem cells within the bone marrow undergo distinguishable stages of B cell differentiation (Figure 1) [4-6]; pro-B cells develop into pre-B and finally immature/transitional B cells. Transitional B cells are the first B cells to leave the bone marrow; they migrate to the spleen where they differentiate into either IgM memory (antigen independent) or mature B cells. Mature B cells migrate to the primary follicle of the lymph nodes and spleen, forming the germinal center (GC) upon antigen exposure. They

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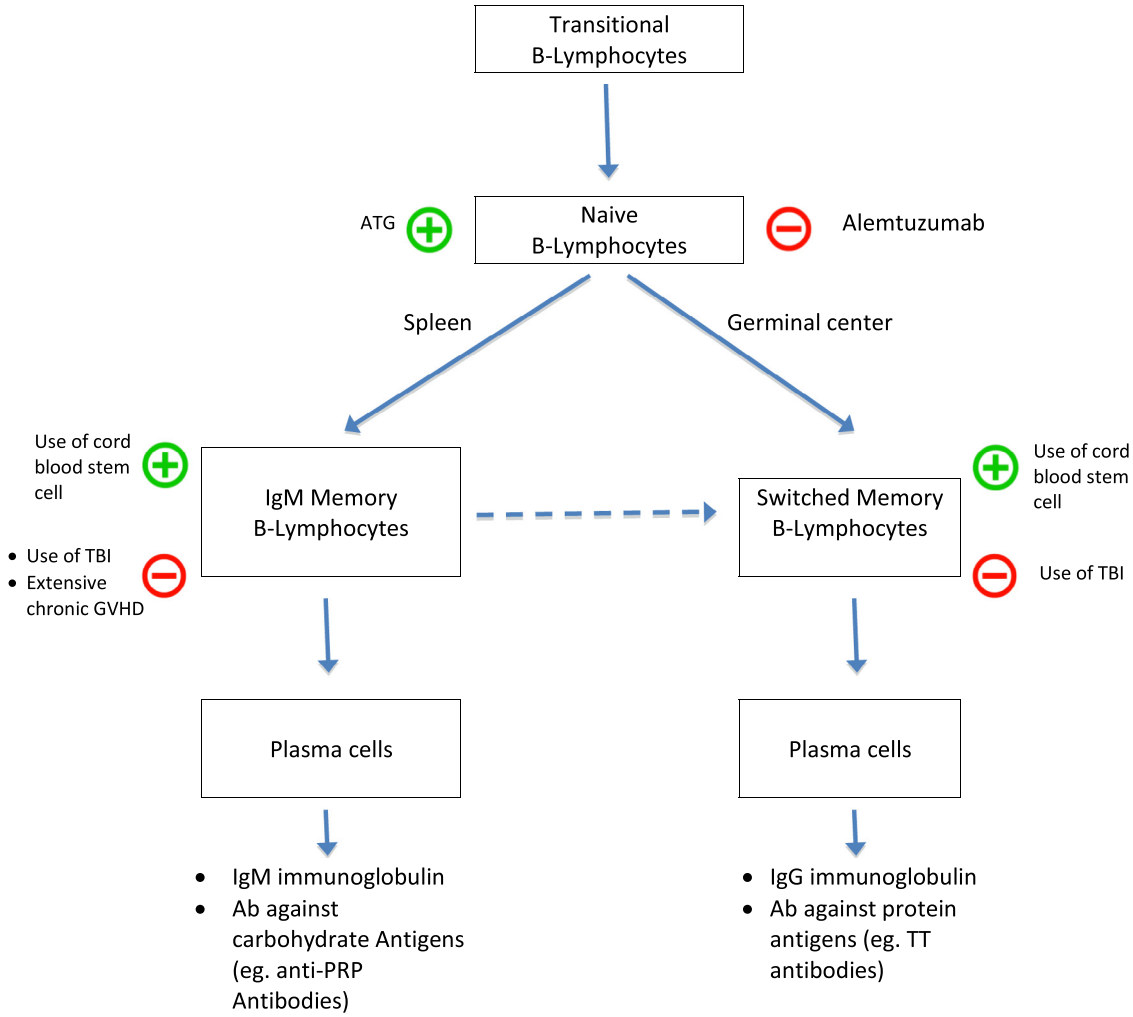

Figure 1. B lymphocyte maturation. Transitional B lymphocytes are the first B lymphocytes to leave the bone marrow, and when they reach the spleen, they can develop into either naive or IgM-memory B lymphocyte. Transitional B lymphocytes express toll-like receptor-9, which upon exposure to unmethylated bacterial DNA (CpG) can generates IgM memory B lymphocytes. Naive B lymphocytes leave the spleen and after antigen exposure in the germinal center can develop into switched memory and plasma B lymphocytes. Switched memory B lymphocytes, require T lymphocyte costimulation to produce high-affinity antibodies, including IgG and IgA, within the germinal centers of lymphoid tissues. On the other hand, IgM memory B lymphocytes are similar to marginal zone B cells in the spleen and respond to infections or vaccination by producing low-affinity IgM antibody.

can then differentiate into either switched memory B cell or plasma cells as an (antigen-dependent) adaptive immune response occurring in the GC.

A deficiency of naive B cells after allo-HSCT in the setting of high amounts of B cell–activating factor has been associated with the development of cGVHD [7-9]. Moreover, a deficiency of regulatory B was recently shown to also be involved in the pathogenesis of cGVHD [10]. Allo-HSCT recipients with delayed humoral immune reconstitution have an increased risk of cGVHD [7]. An impaired ability to generate antibodies against carbohydrate antigens may increase the risk for infection, particularly by encapsulated organisms; persistent stimulation by alloantigen and infectious and inflammatory signals, together with naive B cell lymphopenia, makes the achievement of B cell tolerance more challenging and may increase the risk of cGVHD [11-25].

In this study, we assessed the kinetics of humoral immune reconstitution for each stage of B cell development after allo-HSCT among pediatric patients. We also evaluated whether variables such as the use of total body irradiation (TBI), intensity of preparative regimen, source of hematopoietic stem cells, presence of GVHD, or the use of serotherapy (antithymocyte globulin [ATG] or alemtuzumab) were associated with delays in humoral immune reconstitution.

METHODS

We conducted a retrospective analysis among 90 recipients who received allo-HSCT and were followed at Children's Hospital of Los Angeles between 2004 and 2011. Consecutive patients provided consent, in accordance with the Declaration of Helsinki, to participate in a late effects registry. Of the 90 recipients, 19 were excluded because of graft failure (n = 5), disease relapse before engraftment (n = 4), loss to follow-up (n = 5), not having sufficient immune reconstitution data available for analysis because of disease relapse before 6 months after allo-HSCT (n = 3), or receiving rituximab after allo-HSCT (n = 2). All laboratory assessments were done at Children's Hospital of Los Angeles' clinical immunology and flow cytometry laboratory as part of clinical care. The following laboratory assessments were conducted longitudinally and compared with normal clinical laboratory values generated from healthy controls: naive ($IgD^+CD27^-CD19^+$), IgM-memory ($IgD^+CD27^+CD19^+$), and switched memory ($IgD^-CD27^+CD19^+$) B cells; T cell subtypes ($CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD4^+CD25^+CD127dim$ (T regulatory [Tregs]), RA^+CD4^+); and quantitative Ig levels and antibodies (IgG) to both polysaccharide carbohydrate (PRP) and tetanus toxoid (TT) antigens. Normal median and ranges for the B cell subsets are based on our clinical laboratory normal ranges for population younger than 18 years old (n = 63); naive B