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Elevated Numbers of Immature/Transitional CD21$^-$ B Lymphocytes and Deficiency of Memory CD27$^+$ B Cells Identify Patients with Active Chronic Graft-versus-Host Disease

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ABSTRACT

Chronic graft-versus-host disease (cGVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT) and a leading cause of non-relapse mortality (NRM). Currently, biology-based markers are lacking both for diagnosis and for monitoring the activity of cGVHD. Seventy patients who received HSCT were enrolled in a pilot study, including 21 without cGVHD and 49 with active or resolved cGVHD. Evaluations were comprised of clinical parameters including cGVHD severity and infections. Peripheral blood cells were analyzed by multi-parameter flow cytometry. The CD19$^+$ B cell compartment was further subdivided by staining for surface IgD, CD21 and CD27. No significant differences in absolute B, T, and natural killer (NK) cell numbers were observed between the groups with and without cGVHD. However, elevated numbers (>15% of B lymphocytes) of immature/transitional CD19$^+$/CD21$^-$ B cells were associated with the occurrence of severe infections (P = .003). Most significantly, all patients with active cGVHD and elevated numbers of CD19$^+$/CD21$^-$ B lymphocytes experienced severe infections (P = .00016). The numbers of both non-class-switched and class-switched memory B cells were significantly lower in patients with active cGVHD when compared to patients who never experienced cGVHD (P = .002 and P = .001). Perturbation of circulating B lymphocyte compartments may serve as a novel biomarker for monitoring cGVHD activity and its impact on the immune system. A prospective study on unselected patients assessed serially for B cell reconstitution after HSCT is warranted.
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KEY WORDS

chronic GVHD • immature/transitional and memory B lymphocytes

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a major late complication of allogeneic hematopoietic stem cell transplantation (HSCT) and occurs in 30% to 80% of patients [1]. It varies in severity and clinical course; cGVHD is the leading cause of nonrelapse mortality (NRM) more than 2 years after transplantation [2,3]. After HSCT, immune reconstitution occurs gradually over time [4,5]. Immune reconstitution is known to be slower for human leukocyte antigen (HLA)-mismatched [6] or T cell depleted grafts [7], and in survivors with cGVHD [8].

The pathophysiology of cGVHD is still poorly understood [9]. The importance of autoreactivity is suggested by clinical manifestations of cGVHD that frequently mimic those of autoimmune diseases [10], and by the finding of auto-antibodies derived from B cells after T helper type 2 (TH2) mediated stimulation and cytokine release [11]. Recently, chimeric anti-CD20-antibody therapy was reported to be effective

for resistant cGVHD; this supports the hypothesis that distinct B cells or B cell subsets might be directly pathogenic in cGVHD [12,13]. Another probable mechanism for cGVHD is dysfunctional T cell selection in the thymus inducing autoimmune diseases [14]. Functional asplenia, with elevated numbers of erythrocytes bearing Howell-Jolly bodies (HJ) as the hallmark, was observed in patients with cGVHD [15]. Asplenia also affects homeostasis of memory B lymphocytes circulating in the peripheral blood (PB) [16].

In general, B cell development is a stepwise process. B cell precursors are generated in the bone marrow (BM) and migrate to the periphery at the immature/transitional $CD19^+/CD21^-$ B cell stage when they are still short-lived and functionally immature [17]. Immature/transitional B cells are transported via the blood vessels to the spleen, where they develop into long-lived mature B cells ($CD19^+/CD21^+$). This developmental step is critically dependent on the presence of a mature B cell receptor [18] and on tightly regulated additional survival signals brought about by transmembrane proteins such as B cell activation factor from the tumor necrosis factor family (BAFF) [19]. Mature B cells re-circulate between the lymphoid follicles of spleen and lymph nodes, and they play a major role in the adaptive immune response. Significantly, in the initial phases of infection and before specific antibody production commences, natural antibodies limit the spread of pathogens. Subsequently, the antigen-specific, neutralizing antibody response clears cytopathic infections [20]. In fact, all vaccines that are clinically efficient today are dependent on neutralizing antibody responses (rather than T cell-mediated immunity). This demonstrates the unique importance of B cells and their products for protective immunity [20].

Hence, the in-depth analysis of the composition of major B cell sub-populations within a group of patients who underwent HSCT should provide important insights into the patients' level of clinically relevant protective immunity and thus, their overall immunocompetence. This knowledge would especially be warranted in situations where the post-transplant immune system is compromised by ongoing immune responses, such as in cGVHD.

We performed a pilot trial to analyze leukocyte populations in PB and we focused on the homeostasis of major B cell subpopulations. We studied CD21 negative immature/transitional B lymphocytes [21,22], which are known to be increased in autoimmune diseases, ie SLE [23], and in primary and secondary immunodeficiencies, such as common variable immunodeficiency [24] and advanced stages of HIV [25]. Furthermore, we analyzed the CD27 positive memory B lymphocyte compartment, which harbors the direct precursors of immunoglobulin secreting B cells [26,27].

No significant differences in absolute B, T, and natural killer (NK) cell numbers between the groups with and without cGVHD were seen. However, in patients with >15% immature/transitional $CD19^+/CD21^-$ B cells, significantly more severe infections after HSCT were observed as compared to patients with low $CD19^+/CD21^-$ B cell counts. The number of both class-switched and non-class-switched memory B cells was significantly lower in patients with active cGVHD compared to patients never experiencing cGVHD in our pilot study. In summary, B lymphocyte subsets might represent novel biomarkers for the assessment of cGVHD activity and its impact on the immune system seen as increased susceptibility to severe infections. Our preliminary findings should be evaluated prospectively in patients after HSCT.

METHODS

Trial Conduct

During February 2005, all patients with active cGVHD from the Outpatient Clinic of the Bone Marrow Transplant (BMT) Facility who had routine follow-up visits were asked participate. Study inclusion criteria were complete multi lineage donor cell engraftment, being at least 100 days after allogeneic HSCT, available data on all follow-up visits since discharge after HSCT, and written informed consent. Of these 26 patients sampled, 4 were later considered to have resolved cGVHD at the time of sampling whereas 22 had active cGVHD. After observing the disturbance in B cell homeostasis another 44 patients were asked to join the study in September 2005 and they participated after signing the informed consent. This group included 13 patients with active cGVHD, 10 with resolved cGVHD, and 21 who had never experienced cGVHD. All of these patients were seen in the Outpatient Clinic of the BMT Facility for routine follow-up visits. During the sampling period of February to September 2005, only the following patients were excluded: those who missed follow-up visits; were unable to understand the germane informed consent; refused to participate in the study; with unmeasurably low B-cell numbers; or with a relapse of hematological disease. A total of 70 patients were enrolled into this pilot study that had been approved by the local institutional review board (IRB). The study was conducted in accordance with the declaration of Helsinki. In addition to the analysis of leukocyte subpopulations, blood counts, C-reactive protein, and serum immunoglobulin levels were assessed during routine follow-up examinations of patients. Examinations were done at least weekly during the first 100 days after HSCT, monthly until day 365 after HSCT, then every 3 months for 2 years, followed by every 6 months thereafter.

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