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**ORIGINAL ARTICLE**

# Chronic graft-versus-host disease: focusing on the B cells

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## ABSTRACT

Graft-versus-host disease (GVHD) has posed many challenges in allogeneic HSCT. Thanks to the development of immunomodulating approaches, the mortality of acute GVHD (aGVHD) is drastically decreased. Nevertheless, chronic GVHD (cGVHD) is became the leading causes of death in patients who survived of aGVHD. Various studies have demonstrated the essential role of B cells in the development of cGVHD. B cells are directly involved in allogeneic reactions through a variety of mechanisms such as alloantibody production, triggering complement system, promoting antibody-dependent cellular cytotoxicity (ADCC), and cross-presentation of immune complexes. It has been known that the pathways involved in the B-cell homeostasis and survival, such as BAFF, BCR, and Notch2 signaling pathways are abnormal in cGVHD. Post-HSCT lymphopenia triggers the continuous release of BAFF, leading to abnormalities in B cell homeostasis, and increasing the survival of alloreactive/autoreactive B cells, leading to production of allo/auto-antibodies. On the other hand, reduction of regulatory B cells following HSCT, causes loss of T cell peripheral tolerance, leading to cGVHD incidence. Therefore, B cells deserve special consideration in allogeneic HSCT, and targeting alloreactive B cells might be a promising approach in cGVHD management. In this article, we discussed the role of B cells in pathophysiology of cGVHD.

**Keywords:** Chronic graft-versus-host disease, Hematopoietic stem cell transplantation, B cell, BAFF

## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potential solution in the treatment of many hematologic and immunologic disorders (1, 2). However, graft-versus-host disease (GVHD) is one of the most important challenges of allo-HSCT that causes significant morbidity and mortality in patients (3). GVHD could be manifested early after HSCT with a multiple symptoms of inflammation which is called acute GVHD (aGVHD). Generally, aGVHD is caused by the formation of an inflammatory cascade of active allure T cells (3). Thanks to the development of immunomodulatory drugs, the incidence of aGVHD has decreased significantly (4). Chronic GVHD (cGVHD), however, needs more time to develop, and is harder to prevent and cure. It occurs within a year and with an average time of 5 months after allo-HSCT. Up to 70% of aGVHD survivors might experience cGVHD (5). Symptoms of cGVHD vary in terms of involvement of various organs in the body. An important consequence of this disease is the lack of immune tolerance, leading to autoimmune manifestations in the skin, mouth, liver, eyes, lungs, gastrointestinal tract, hematopoietic system and joints (6-9). According to National Institutes of Health (NIH) diagnostic criteria, cGVHD is associated with inflammation, fibrosis, and cellular and humoral immune disorders, and the involvement of various organs, leading to symptoms such as Sika syndrome, cutaneous sclerosis, pulmonary involvement and manifestations of autoimmune diseases (10).

Poikiloderma, lichen planus, obliterans bronchiolitis syndrome, skin depigmentation, sclerosis, lung involvement, esophageal web, gastrointestinal involvement, fasciitis, joint stiffness and myositis are some of the manifestations of cGVHD (11). Besides, cryptogenic organizing pneumonia (COP), thrombocytopenia, and pancreatic atrophy are considered as other symptoms of cGVHD (8). However, weight loss syndrome, anorexia, gingivitis, maculopapular rash, erythema and liver dysfunction are also common among cGVHD patients but are not part of the NIH diagnostic criteria (11).

If involvement of $\leq$2 organs with a score of 1 occurs, cGVHD is mild; if involvement of $\geq$3 organs occurs with a score of $\geq$1, or involvement of lung occurs with a score of 1-2, cGVHD is moderate. Finally, the involvement of one organ with a score of three or involvement of lung with the score greater than 2 is considered severe cGVHD. Therefore, pulmonary involvement usually increases the severity score (6, 10).

The well-known risk factors for cGVHD include age and sex of patients and donors, type of underlying disease, history of aGVHD and its grade, serological status of CMV, difference in HLA, source of stem cells, cell components of graft, use of Total body radiotherapy (TBI), conditioning regimen, and GVHD prophylaxis regimen (12-14).

**Pathophysiology of cGVHD:** Although it has been known that the human major histocompatibility complex (MHC) or Minor histocompatibility antigen (mHA) antigens are major alloantigens triggering both aGVHD and cGVHD (15), the pathophysiology of cGVHD is not clear enough (6). The lack of efficient animal models is the most important cause of data paucity in cGVHD mechanism. Besides, existing mouse models such as sclerotic model and autoantibody-producing models are not able to cause complex pathological manifestations of cGVHD (16, 17). The fact that cGVHD often occurs in patients with a history of aGVHD probably suggests that T cells play a critical role in the pathogenesis of cGVHD (18). The immunosuppressive treatment for the prevention of aGVHD suppress the activation of alloreactive donor T cells. Following the taper

in immunosuppressive regimen, the delayed activation of alloreactive donor T cells results in the development of cGVHD. However, despite aGVHD, Th2 cytokines appear to play a prominent role in cGVHD (19).

Interestingly, the manifestations of cGVHD differ from aGVHD, and are similar to autoimmune disorders such as Systemic lupus erythematosus (SLE), lichen planus, bronchiolitis obliterans syndrome, primary biliary cirrhosis, and autoimmune cytopenia (19, 20). Furthermore, cGVHD shared laboratory findings with autoimmune disorders. It has been found that in cGVHD there is a high prevalence of autoantibodies against double-stranded DNA and smooth muscle (20). Studies have shown a strong association between autoantibodies such as anti-DBY and antibodies against intermediate filament of cytoskeleton with clinical manifestations and the severity of cGVHD (21). Such extensive similarity of cGVHD to autoimmune disorders has made it a complex and heterogeneous disease. Some researchers believe that the same tissue damage occurs in both cGVHD and autoimmune disease. The difference is that the damage in cGVHD is caused by T cells activated by the chronic stimulation with tissue compatibility antigens, while in autoimmune disorders, it is caused by T cells stimulated with non-polymorphic antigens (22). There is even an idea that suggest non-polymorphic antigens involved in autoimmune diseases as antigenic targets in cGVHD (22).

On the other hand, notwithstanding the advances in the T cell suppressive therapies, the incidence of cGVHD is still high, suggesting the role of other immune cells in the development of cGVHD (22). Various studies have proposed B cells as the major player in the development of this complex disease. The BCR sequencing also shows that CDR3 of the IgG antibodies has allo/autoreactive properties and could possibly be considered as an antigenic target in cGVHD (23). Herein, we discussed the role of B cells in the pathophysiology of cGVHD.

**Development of B cell tolerance after allo-HSCT:** B cell differentiation occurs through a highly dynamic and regulated process in which the autoreactive B cells are removed, while those clones that are not severely reacted with self-antigens are positively selected (19). In healthy individuals, B cell development begins with the production of pre-cursor B cells in the bone marrow (BM). Despite central tolerance in BM, large amounts of polyreactive and autoreactive transient B cells migrate from BM to the periphery (18). Clonal deletion, anergy, and receptor editing in the BM cannot delete all autoreactive B cell clones. Thus, approximately 50-75% of transient B cells in healthy adults are autoreactive that should be deleted in the periphery (19).

The differentiation and survival of B cells are tuned by B cell-activating factor (BAFF) (24). BAFF is a cytokine belonging to the tumor necrosis factor (TNF) superfamily (24). It is mainly produced by mononuclear cells in the peripheral blood, lymph nodes, and spleen. BAFF binds to BAFF receptor (BAFF-R) on the surface of B cells, enhancing B cell proliferation (24). Autoreactive B cells are highly BAFF-dependent. The low concentration of BAFF in the circulation is not sufficient to support autoreactive B cells survival and ultimately leads to their deletion (25). In contrast, high levels of BAFF enhance the differentiation and survival of autoreactive B cells (20, 25).

Following allo-HSCT, donor B cells are transferred to the recipient, but the number of pre-cursor B cells and naiive B cells is low leading to a transient lymphopenia until these cells regenerate in the recipient (21). Lymphopenia triggers the continuous release of BAFF, leading to abnormalities in B cell homeostasis, and thus, increasing the survival of alloreactive and autoreactive B cells (21). These remaining autoreactive B cells can participate in primary immune responses and differentiate to short-lived plasma cells. However, they are unable to participate in germinal center (GC) reactions, which is why B cells after HSCT have limited variety in BCRs and produce low-affinity allo/auto-antibodies (18, 25). Similarly, in autoimmune disorders, an abnormal increase in BAFF reduces BCR-induced apoptosis in autoreactive B cells. Altogether, the high level of BAFF following HSCT-induced lymphopenia cause the survival of autoreactive B cells (20, 26).

**Abnormal B cell homeostasis in cGVHD:** It has been known that the pathways involved in the B-cell homeostasis and survival, such as BAFF, BCR, and Notch2 signaling pathways are abnormal in cGVHD (20).

As mentioned, post-HSCT lymphopenia induces BAFF release. High levels of BAFF cause the survival of allo/autoreactive B cells, leading to production of allo/auto-antibodies (20, 25).

The continuous high level of BAFF along with the slow differentiation of naïve B cells are associated with cGVHD (26). Increasing BAFF in active cGVHD causes long-term survival of B cells and increases the signaling pathways of AKT and ERK (26). Activation of protein kinase B (PKB/AKT) pathway enhances B cell metabolism, and simultaneous activation of the AKT and extracellular signal-regulated kinase (ERK) pathways destroys the pro-apoptotic BIM or BCL2L11 protein, resulting in B cells becoming resistant to apoptosis (20).

Another impaired signaling pathway in cGVHD is the BCR pathway. Upon binding of antigens to the BCRs, phosphorylation and activation of tyrosine kinase spleen associated tyrosine kinase (Syk) occurs, which subsequently phosphorylates and activates the B cell linker protein (BLNK) adapter protein (27). BLNK, as an anchor protein for Bruton's tyrosine kinase (BTK) and phospholipase (PL)Cγ2, plays a key role in BCR signaling. Syk inhibitors such as fostamatinib inhibit the BCR-mediated activation of B cells, and thereby, reduce the incidence of tissue damages caused by cGVHD (27). The other BCR signaling pathway molecule that has been shown to play an important role in the pathogenesis of cGVHD, is Notch2 (28). Notch2 is a transmembrane molecule involved in aberrant BCR signaling in patients with cGVHD (28). BCR over-responses as a result of increased Notch2 signaling activity enhances BLNK expression. It has also been shown that in cGVHD patients there is an increase in the Notch2-BCR signaling pathway and a decrease in interferon regulatory factor (IRF)4/IRF8 expression (28). Interestingly, inhibition of the Notch2-BCR axis by monoclonal antibodies (mAbs) in cGVHD suppresses B cell aberrant activity but maintains physiological humoral immune responses (28).

**Possible roles of B cells in the development of cGVHD:** Under homeostatic conditions, several mechanisms inhibit the function of pathogen B cells through central and peripheral tolerance. In patients undergoing allo-HSCT, thymus dysfunction due to aging, effects of conditioning regimens, and calcineurin inhibitors may result in defective T cell tolerance (17). Besides, auto/alloreactive B cells could aggravate the unwanted immune reaction promoting cGVHD. B cells are involved in complement activation, ADCC process, and antigen presentation to TCD4 + and TCD8 + cells (Fig. 1). High level of auto/alloreactive B cells along with reduction in regulatory B cells might also cause loss of peripheral T cell tolerance and development of cGVHD (29).

It has been revealed that the infiltration of CD4+ T cells, and B220 B cells as well as alloantibody deposition are involved in lung and liver fibrosis in cGVHD. Besides, the elevation of follicular helper T cells (Tfh), germinal center-B cells and macrophages is required for cGVHD development (17, 30, 31). Contrarily, in HSCT patients who have not manifested cGVHD, a large number of naïve B cells and transient B cells are required in the peripheral blood to completely neutralize BAFF, and efficiently remove alloreactive and autoreactive B cells (21).

B cell phenotypes appear to be significantly different in patients with cGVHD from non-cGVHD patients. It has recently been found that the number of common lymphoid progenitors, pro-B, pre-B, and immature B cells in the bone marrow of bronchiolitis obliterans syndrome (BOS) mouse models, that manifested a similar reaction to cGVHD, is low (32). Also, niche of B cells is misplaced in this model, leading to the disruption in the maturation and development of B cells. The delay in the reconstitution of CD19+ IgD CD38low CD27+ naïve B cells is the reason for their relative low count in cGVHD patients (32).

Elevated BAFF levels are associated with an increase in the number of pre-germinal center (GC) B cells (IgD+ CD38high CD27+) and post-GC plasma like cells (IgDlow CD38hi CD27+), exacerbating the cGVHD condition (33). These CD27+ cells can produce antibodies without the need for BCR stimulation or any secondary signals (33). Therefore, it is hypothesized that these cells may mediate responses against the host organs through an antigen-independent pathway.

It has been postulated that the high levels of BAFF combined with low naïve B cell counts may increase the lifespan of alloreactive and autoreactive B cells, leading to pathological and immunological reactions in cGVHD (21, 34).

**The role of regulatory B cells in the development of cGVHD:** Regulatory B (Breg) cells produce IL-10 suppressing the autoimmunity in mice and humans. Studies have shown that the decrease in the number of Breg cells or defects in their function are associated with the severity in cGVHD. It is reported that Breg cells deficiency to produce IL-10 is probably due to disruption of the signal transducer and activator of transcription 3 (STAT3) and ERK2 signaling pathways (27, 35, 36). IL-10 production is not limited to Breg cells. The CD24(hi) CD27(+) B cells and CD27(hi) CD38(hi) plasmablasts are also the source of IL-10.

It has been reported that in allo-HSCT recipients, the regeneration of memory Breg cell treasures is impaired and patients with cGVHD have less amount of IL-10 producing CD24(hi), CD27(+) B cells. Although cGVHD patients have shown an increase in the number of plasmablasts, the number of IL-10 producing plasmablasts are significantly low (36).

To sum up, it seems that IL-10 producing CD24(hi) CD27(+) B cells and Breg cells have a prominent role in the prevention of cGVHD.

**B cell-related cGVHD biomarkers:** CGVHD biomarkers are divided into diagnostic, predictive, and prognostic groups, including plasma mediators, antibodies, inflammatory cells, and gene polymorphisms (37).

Studies have shown that plasma BAFF levels can be used as a predictor of non-relapse mortality (NRM) in cGVHD patients (20). The elevated level of Chemokine (C-X-C motif) ligand 9 (CXCL9) and high-molecular-weight adiponectin are reported to be associated with cGVHD severity (20). Antibodies such as anti-HY and anti-platelet-derived growth factor receptor (PDGFR) are distinct biomarkers for alloimmunity in cGVHD (38).

Changes in the immune cells are could be serve as cGVHD biomarker. It has been revealed that the decreased Breg cells count and altered Treg cell homeostasis are prognostic biomarkers in cGVHD patients (20). On the other hand, studies have shown that CD19+ CD10+ transitional B cells not only can be used as a biomarker in the diagnosis of cGVHD but also has the ability to predict cGVHD-mediated complications such as cGVHD-dependent gamma globulinemia or bronchiolitis obliterans syndrome (39). Kappa-deleting recombination excision circles (KRECs) is a useful biomarker to evaluate the mechanism and dynamics of B cell reconstitution. It can be used to investigate the history of B cell proliferation due to the positive correlation between KREC and the number of B cells after transplantation (39).

**Treatment of cGVHD: targeting B cells:** cGVHD is a multi-organ disease for which the treatment of choice is immunosuppressive agents. Steroids are commonly used as the first line of treatment for moderate to severe cGVHD (40). For steroid-refractory cases a second line of treatment is needed. Based on clinical trials, the response rate to the second line of treatment is 25-50%, but no treatment has a significant advantage over the other. Therefore, the choice of treatment depends on patients' factors such as the underlying disease and the organ involved.

Kinase inhibitors (genus kinase inhibitors, roxolitinib, baricitinib, ibrotinib, syk inhibitors and Rho kinase inhibitors), cytokine regulators (IL-2), inhibitors Proteasome (bortzomib, Carfilzomib, Ixazomib), immune and metabolic checkpoint blockade, and Adoptive cell therapy (Tregs, MSCs) are among the second-line treatment options for cGVHD (14, 23, 41-51). Noteworthy, all of the above mentioned drugs are immunosuppressive which increase the risk of serious, severe, and life-threatening infections. Given the critical role of B cells in the pathophysiology of cGVHD, targeting B cells could be a promising approach to control the cGVHD.

Table 1. B cell Targeting in chronic GVHD

| Target | Function | Targeted therapy | Effect in cGVHD | Ref. |
|---|---|---|---|---|
| BTK and ITK | BCR activation | Ibrutinib | • FDA-approved irreversible inhibitor of BTK and ITK<br>• Targets Th2 cells and B cells<br>• Produces durable remissions in B cell abnormalities<br>• Minimal toxicity | (60, 61) |
| IL-6 receptor | Proliferation of pre–B cells | Tocilizumab | • Increases OS<br>• Increases Relapse Free Survival<br>• Salvage therapy in severe cGVHD | (62) |
| CD20 | B-cell surface antigen | Rituximab | • B cell depletion leading to the suppression of activated Tfh cells<br>• Safe and effective for first-line treatment of cGVHD | (34, 52, 63) |
| CD30 | Expressed on activated B cells<br>Positive regulator of apoptosis | Brentuximab | • Effective in the treatment of steroid-refractory cGVHD<br>• Treatment-emergent toxicities, including peripheral neuropathy | (64) |
| JAK 1/2 | Effects on cytokine and chemokine receptors in B cells | Ruxolitinib | • Treatment option for steroid-refractory aGVHD and cGVHD | (23) |
| SYK | BCR activation<br>Cell migration<br>Endocytosis | Entospletinib<br>Fostamatinib | • Effective at inducing apoptosis in human cGVHD B cells | (65) |
| ROCK2 | B-cell migration<br>T-cell activation with pSTAT3/5 effects | KD025 (belumosudil) | • Clinical trials are ongoing | (66) |
| Proteasome | Regulation of proteins | Carfilzomib<br>Bortezomib | • 80% overall response<br>• 10% complete response<br>• A feasible and well tolerated initial treatment of cGVHD (combined with prednisone)<br>• Carfilzomib did not improve expected 6-month treatment failure rates | (67, 68) |
| Plasma cells | Immunoglobulin production leading to organ damage | Pomalidomide | • Clinical trials are ongoing | (69) |

BTK. Bruton's tyrosine kinase; ITK. Interleukin-2-inducible T cell kinase; BCR. B cell receptor; OS. Overall survival; Tfh. T follicular helper cells; SR-GVHD. Steroid refractory graft versus host disease; JAK. Janus kinase; SYK. Spleen tyrosine kinase; ROCK2 Rho-associated kinase 2;

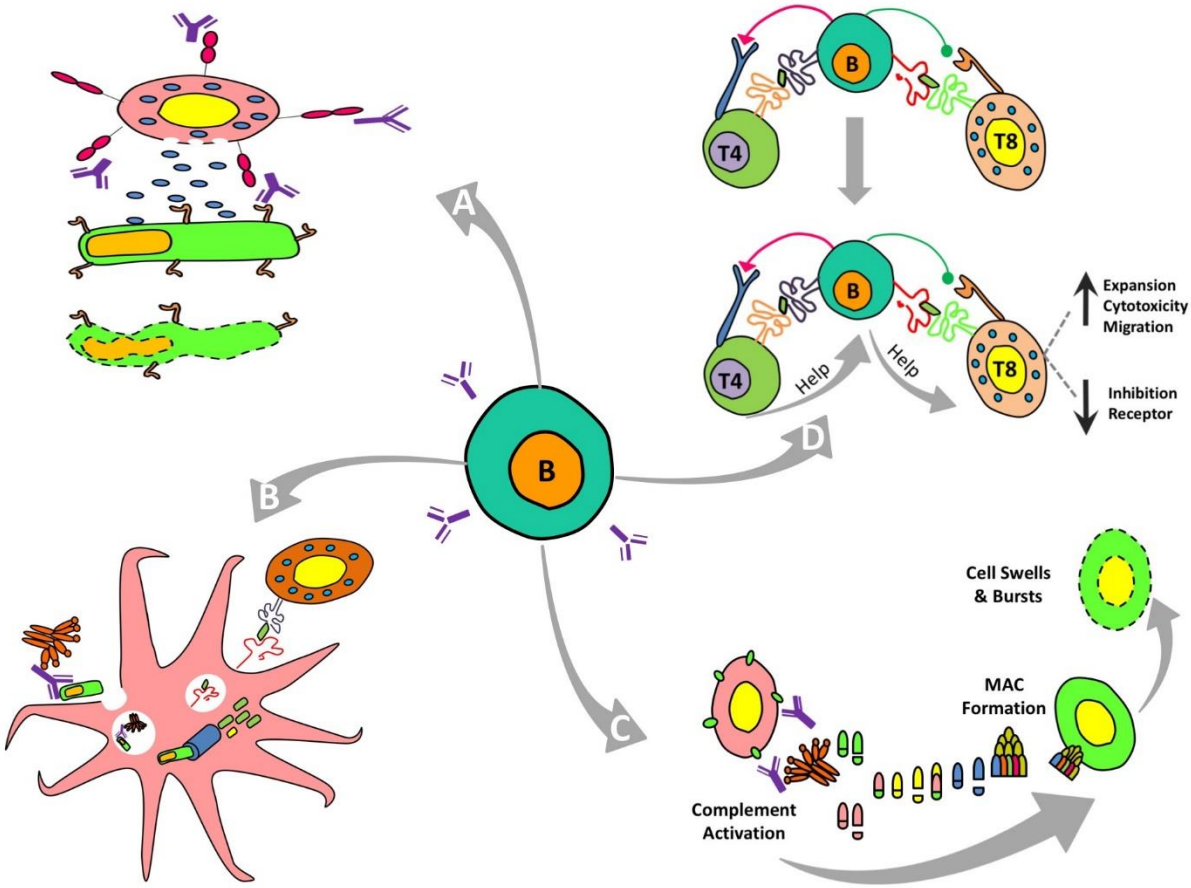


Figure 1. Possible roles of B cells in the development of cGVHD. B cells are involved in ADCC process (A), cross presentation of immune complexes (B), complement activation (C), and are involved in priming TCD4 + and TCD8 + cells by antigens presentation (D).

B cell-targeted therapies can be classified as (1) B cell depletion by antibodies, (2) modulation of BAFF-R signaling, and (3) inhibition of BCR signaling. First, CD20 in B cells can be targeted by rituximab or ofatumumab, leading to B cell depletion (52-55). Second, since Syk and NFκB are activated in BAFF-R pathway, their inhibition by fostamatinib and bortezomib could modulate the survival of autoreactive B cells. Finally, BCR response activates SyK, BTK, and BLNK signaling, leading to the activation of ERK and NFκB (21, 26, 27). BTK can be inhibited by TKIs such as ibrutinib (56-58). In addition, T follicular helper (TFH) cells can involve in formation of germinal center and B cell maturation by producing IL-21 (59).

Increase in the TFH cells is accompanied with increased GC B cells and development of cGVHD in experimental models. Ibrutinib and fostamatinib can inhibit ITK and SyK in TFH, respectively, leading to the modulation of the B cell development in GC (Table 1) (6).

## CONCLUSION

Various studies have demonstrated the essential role of B cells in the development of cGVHD. B cells are directly involved in allogeneic reactions through a variety of mechanisms such as alloantibody production, triggering complement system, promoting antibody-dependent cellular cytotoxicity (ADCC), and cross-presentation of immune complexes. These cells are also indirectly involved in cGVHD reactions by priming CD4+ T cells and CD8+ T cells. It has been known that the pathways involved in the B-cell homeostasis and survival, such as BAFF, BCR, and Notch2 signaling pathways are abnormal in cGVHD. Post-HSCT lymphopenia triggers the continuous release of BAFF, leading to abnormalities in B cell homeostasis, and thus, increasing the survival of alloreactive and autoreactive B cells, leading to production of allo/auto-antibodies. On the other hand, reduction of regulatory B cells following HSCT, causes loss of T cell peripheral tolerance, leading to cGVHD incidence. Therefore, B cells deserve special consideration in allogeneic HSCT, and targeting alloreactive B cells might be a promising approach in cGVHD management.

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## REFERENCES

1. Ardakani MT, Mehrpooya M, Mehdizadeh M, Beiraghi N, Hajifathali A, Kazemi MH. Sertraline treatment decreased the serum levels of interleukin-6 and high-sensitivity C-reactive protein in hematopoietic stem cell transplantation patients with depression; a randomized double-blind, placebo-controlled clinical trial. Bone marrow transplantation. 2020;55(4):830-2.
2. Hajifathali A, Parkhideh S, Kazemi MH, Chegeni R, Roshandel E, Gholizadeh M. Immune checkpoints in hematologic malignancies: What made the immune cells and clinicians exhausted! Journal of cellular physiology. 2020;235(12):9080-97.
3. Momeni-Varposhti Z, Kazemi MH, Talebi M, Chegeni R, Roshandel E, Hajifathali A, et al. Plasma levels of norepinephrine and expression levels of ß2-adrenergic receptor gene correlate with the incidence of acute graft-versus-host disease. Medical Journal of the Islamic Republic of Iran. 2020;34:151.
4. Ghasemi K, Parkhideh S, Kazemi MH, Salimi M, Salari S, Nalini R, et al. The role of serum uric acid in the prediction of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Journal of clinical laboratory analysis. 2020;34(7):e23271.
5. MacDonald K, Hill GR, Blazar BR. Chronic graft-versus-host disease: biological insights from preclinical and clinical studies. Blood. 2017;129(1):13-21.
6. Nakasone H, Sahaf B, Miklos DB. Therapeutic benefits targeting B-cells in chronic graft-versus-host disease. International journal of hematology. 2015;101(5):438-51.
7. Nakasone H, Onizuka M, Suzuki N, Fujii N, Taniguchi S, Kakihana K, et al. Pre-transplant risk factors for cryptogenic organizing pneumonia/bronchiolitis obliterans organizing pneumonia after hematopoietic cell transplantation. Bone marrow transplantation. 2013;48(10):1317-23.
8. Maedler-Kron C, Marcus VA, Michel RP. Hematopoietic stem cell transplantation. Pathology of Transplantation: Springer; 2016. p. 401-49.
9. Nakasone H, Fukuda T, Kanda J, Mori T, Yano S, Kobayashi T, et al. Impact of conditioning intensity and TBI on acute GVHD after hematopoietic cell transplantation. Bone marrow transplantation. 2015;50(4):559-65.
10. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. Biology of Blood and Marrow Transplantation. 2015;21(3):389-401. e1.
11. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biology of blood and marrow transplantation. 2005;11(12):945-56.
12. Lamarthée B, Malard F, Gamonet C, Bossard C, Couturier M, Renauld J-C, et al. Donor interleukin-22 and host type I interferon signaling pathway participate in intestinal graft-versus-host disease via STAT1 activation and CXCL10. Mucosal immunology. 2016;9(2):309-21.
13. Neurath MF. Current and emerging therapeutic targets for IBD. Nature Reviews Gastroenterology & Hepatology. 2017;14(5):269-78.
14. Fløisand Y, Lundin KE, Lazarevic V, Kristiansen JD, Osnes LT, Tjønnfjord GE, et al. Targeting integrin α4β7 in steroid-refractory intestinal graft-versus-host disease. Biology of Blood and Marrow Transplantation. 2017;23(1):172-5.
15. Hahn T, McCarthy Jr PL, Zhang M-J, Wang D, Arora M, Frangoul H, et al. Risk factors for acute graft-versus-host disease after human leukocyte antigen–identical sibling transplants for adults with leukemia. Journal of Clinical Oncology. 2008;26(35):5728.

16. Blazar B, White ES, Couriel D. Understanding chronic GVHD from different angles. Biology of Blood and Marrow Transplantation. 2012;18(1):S184-S8.
17. Wu T, Young JS, Johnston H, Ni X, Deng R, Racine J, et al. Thymic damage, impaired negative selection, and development of chronic graft-versus-host disease caused by donor CD4+ and CD8+ T cells. The Journal of Immunology. 2013;191(1):488-99.
18. Sarantopoulos S, Blazar BR, Cutler C, Ritz J. B cells in chronic graft-versus-host disease. Biology of Blood and Marrow Transplantation. 2015;21(1):16-23.
19. Cancro MP. Peripheral B-cell maturation: the intersection of selection and homeostasis. Immunological reviews. 2004;197(1):89-101.
20. Li X, Gao Q, Feng Y, Zhang X. Developing role of B cells in the pathogenesis and treatment of chronic GVHD. British journal of haematology. 2019;184(3):323-36.
21. Sarantopoulos S, Ritz J. Aberrant B-cell homeostasis in chronic GVHD. Blood, The Journal of the American Society of Hematology. 2015;125(11):1703-7.
22. Toubai T, Sun Y, Reddy P. GVHD pathophysiology: is acute different from chronic? Best Practice & Research Clinical Haematology. 2008;21(2):101-17.
23. Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia. 2015;29(10):2062-8.
24. Gorelik L, Gilbride K, Dobles M, Kalled SL, Zandman D, Scott ML. Normal B cell homeostasis requires B cell activation factor production by radiation-resistant cells. The Journal of experimental medicine. 2003;198(6):937-45.
25. Thien M, Phan TG, Gardam S, Amesbury M, Basten A, Mackay F, et al. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. Immunity. 2004;20(6):785-98.
26. Allen JL, Fore MS, Wooten J, Roehrs PA, Bhuiya NS, Hoffert T, et al. B cells from patients with chronic GVHD are activated and primed for survival via BAFF-mediated pathways. Blood, The Journal of the American Society of Hematology. 2012;120(12):2529-36.
27. Allen JL, Tata PV, Fore MS, Wooten J, Rudra S, Deal AM, et al. Increased BCR responsiveness in B cells from patients with chronic GVHD. Blood, The Journal of the American Society of Hematology. 2014;123(13):2108-15.
28. Poe JC, Jia W, Su H, Anand S, Rose JJ, Tata PV, et al. An aberrant NOTCH2-BCR signaling axis in B cells from patients with chronic GVHD. Blood, The Journal of the American Society of Hematology. 2017;130(19):2131-45.
29. Dawkins B, Minchinton RM. Fetomaternal alloimmune thrombocytopenia treated with intragam. The Medical journal of Australia. 1999;170(9):451-2.
30. Alexander KA, Flynn R, Lineburg KE, Kuns RD, Teal BE, Olver SD, et al. CSF-1–dependant donor-derived macrophages mediate chronic graft-versus-host disease. The Journal of clinical investigation. 2014;124(10):4266-80.
31. Young JS, Wu T, Chen Y, Zhao D, Liu H, Yi T, et al. Donor B cells in transplants augment clonal expansion and survival of pathogenic CD4+ T cells that mediate autoimmune-like chronic graft-versus-host disease. The Journal of Immunology. 2012;189(1):222-33.
32. Sarantopoulos S, Stevenson KE, Kim HT, Cutler CS, Bhuiya NS, Schowalter M, et al. Altered B-cell homeostasis and excess BAFF in human chronic graft-versus-host disease. Blood, The Journal of the American Society of Hematology. 2009;113(16):3865-74.
33. Sarantopoulos S, Stevenson KE, Kim HT, Bhuiya NS, Cutler CS, Soiffer RJ, et al. High levels of B-cell activating factor in patients with active chronic graft-versus-host disease. Clinical Cancer Research. 2007;13(20):6107-14.
34. Sarantopoulos S, Stevenson KE, Kim HT, Washel WS, Bhuiya NS, Cutler CS, et al. Recovery of B-cell homeostasis after rituximab in chronic graft-versus-host disease. Blood, The Journal of the American Society of Hematology. 2011;117(7):2275-83.
35. Brunstein CG, Miller JS, Cao Q, McKenna DH, Hippen KL, Curtsinger J, et al. Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. Blood, The Journal of the American Society of Hematology. 2011;117(3):1061-70.
36. Socié G. Chronic GVHD: B cells come of age. Blood, The Journal of the American Society of Hematology. 2011;117(7):2086-7.
37. Boukouaci W, Busson M, Peffault de Latour R, Rocha V, Suberbielle C, Bengoufa D, et al. MICA-129 genotype, soluble MICA, and anti-MICA antibodies as biomarkers of chronic graft-versus-host disease. Blood, The Journal of the American Society of Hematology. 2009;114(25):5216-24.
38. Miklos DB, Kim HT, Miller KH, Guo L, Zorn E, Lee SJ, et al. Antibody responses to HY minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood. 2005;105(7):2973-8.
39. Nakatani K, Imai K, Shigeno M, Sato H, Tezuka M, Okawa T, et al. Cord blood transplantation is associated with rapid B-cell neogenesis compared with BM transplantation. Bone marrow transplantation. 2014;49(9):1155-61.
40. Robson NC, Donachie AM, Mowat AM. Simultaneous presentation and cross-presentation of immune-stimulating complex-associated cognate antigen by antigen-specific B cells. European journal of immunology. 2008;38(5):1238-46.
41. Hill L, Alousi A, Kebriaei P, Mehta R, Rezvani K, Shpall E. New and emerging therapies for acute and chronic graft versus host disease. Therapeutic advances in hematology. 2018;9(1):21-46.
42. MacMillan ML, Robin M, Harris AC, DeFor TE, Martin PJ, Alousi A, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. Biology of Blood and Marrow Transplantation. 2015;21(4):761-7.
43. Martin PJ, Rizzo JD, Wingard JR, Ballen K, Curtin PT, Cutler C, et al. First-and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation. 2012;18(8):1150-63.
44. Kirken R, Wang Y, editors. Molecular actions of sirolimus: sirolimus and mTor. Transplantation proceedings; 2003: Elsevier.
45. Couriel D, Saliba R, Escalon M, Hsu Y, Ghosh S, Ippoliti C, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. British journal of haematology. 2005;130(3):409-17.
46. Lutz M, Mielke S. New perspectives on the use of mTOR inhibitors in allogeneic haematopoietic stem cell transplantation and graft-versus-host disease. British journal of clinical pharmacology. 2016;82(5):1171-9.
47. Im A, Hakim F, Pavletic S. Novel targets in the treatment of chronic graft-versus-host disease. Leukemia. 2017;31(3):543-54.
48. Marcondes AM, Hockenbery D, Lesnikova M, Dinarello CA, Woolfrey A, Gernsheimer T, et al. Response of steroid-refractory acute GVHD to α1-antitrypsin. Biology of Blood and Marrow Transplantation. 2016;22(9):1596-601.
49. Roshandel E, Noorazar L, Farhadihosseinabadi B, Mehdizadeh M, Kazemi MH, Parkhideh S. PI3 kinase signaling pathway in hematopoietic cancers: A glance in

miRNA's role. Journal of clinical laboratory analysis. 2021;35(4):e23725.
50. Nalini R, Roshandel E, Mohammadzadeh S, Kazemi MH, Nikoonezhad M, Jalili A, et al. The effect of beta-adrenergic stimulation in the expression of the urokinase plasminogen activator receptor in bone marrow mesenchymal stem cells. Gene Reports. 2021;22:101017.
51. Kazemi MH, Najafi A, Karami J, Ghazizadeh F, Yousefi H, Falak R, et al. Immune and metabolic checkpoints blockade: Dual wielding against tumors. International Immunopharmacology. 2021;94:107461.
52. Cutler C, Miklos D, Kim HT, Treister N, Woo S-B, Bienfang D, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood. 2006;108(2):756-62.
53. Ratanatharathorn V, Logan B, Wang D, Horowitz M, Uberti JP, Ringden O, et al. Prior rituximab correlates with less acute graft-versus-host disease and better survival in B-cell lymphoma patients who received allogeneic peripheral blood stem cell transplantation. British journal of haematology. 2009;145(6):816-24.
54. Arai S, Sahaf B, Narasimhan B, Chen GL, Jones CD, Lowsky R, et al. Prophylactic rituximab after allogeneic transplantation decreases B-cell alloimmunity with low chronic GVHD incidence. Blood, The Journal of the American Society of Hematology. 2012;119(25):6145-54.
55. Pidala J, Kim J, Betts BC, Alsina M, Ayala E, Fernandez HF, et al. Ofatumumab in combination with glucocorticoids for primary therapy of chronic graft-versus-host disease: phase I trial results. Biology of Blood and Marrow Transplantation. 2015;21(6):1074-82.
56. Advani RH, Buggy JJ, Sharman JP, Smith SM, Boyd TE, Grant B, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. Journal of Clinical Oncology. 2013;31(1):88.
57. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. New England Journal of Medicine. 2013;369(1):32-42.
58. Dubovsky JA, Beckwith KA, Natarajan G, Woyach JA, Jaglowski S, Zhong Y, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood. 2013;122(15):2539-49.
59. Flynn R, Du J, Veenstra RG, Reichenbach DK, Panoskaltsis-Mortari A, Taylor PA, et al. Increased T follicular helper cells and germinal center B cells are required for cGVHD and bronchiolitis obliterans. Blood, The Journal of the American Society of Hematology. 2014;123(25):3988-98.
60. Dubovsky JA, Flynn R, Du J, Harrington BK, Zhong Y, Kaffenberger B, et al. Ibrutinib treatment ameliorates murine chronic graft-versus-host disease. The Journal of clinical investigation. 2014;124(11):4867-76.
61. Schutt SD, Fu J, Nguyen H, Bastian D, Heinrichs J, Wu Y, et al. Inhibition of BTK and ITK with ibrutinib is effective in the prevention of chronic graft-versus-host disease in mice. PloS one. 2015;10(9):e0137641.
62. Kattner A-S, Holler E, Holler B, Klobuch S, Weber D, Martinovic D, et al. IL6-receptor antibody tocilizumab as salvage therapy in severe chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. Annals of hematology. 2020;99(4):847-53.
63. Malard F, Labopin M, Yakoub-Agha I, Chantepie S, Guillaume T, Blaise D, et al. Rituximab-based first-line treatment of cGVHD after allogeneic SCT: results of a phase 2 study. Blood, The Journal of the American Society of Hematology. 2017;130(20):2186-95.
64. DeFilipp Z, Li S, Kempner ME, Brown J, Del Rio C, Valles B, et al. Phase I trial of brentuximab vedotin for steroid-refractory chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. Biology of Blood and Marrow Transplantation. 2018;24(9):1836-40.
65. Flynn R, Allen JL, Luznik L, MacDonald KP, Paz K, Alexander KA, et al. Targeting Syk-activated B cells in murine and human chronic graft-versus-host disease. Blood, The Journal of the American Society of Hematology. 2015;125(26):4085-94.
66. Zeiser R, Sarantopoulos S, Blazar BR. B-cell targeting in chronic graft-versus-host disease. Blood. 2018;131(13):1399-405.
67. Pidala JA, Jaglowski S, Im AP, Chen GL, Onstad L, Kurukulasuriya C, et al. Carfilzomib for treatment of refractory chronic GVHD: A Chronic GVHD Consortium Pilot Trial. Biology of Blood and Marrow Transplantation. 2019;25(3):S233.
68. Herrera AF, Kim HT, Bindra B, Jones KT, Alyea III EP, Armand P, et al. A phase II study of bortezomib plus prednisone for initial therapy of chronic graft-versus-host disease. Biology of Blood and Marrow Transplantation. 2014;20(11):1737-43.
69. Yamashita Y, Tamura S, Oiwa T, Kobata H, Kuriyama K, Mushino T, et al. Successful intrathecal chemotherapy combined with radiotherapy followed by pomalidomide and low-dose dexamethasone maintenance therapy for a primary plasma cell leukemia patient. Hematology reports. 2017;9(1).