References


2. Bone Marrow Transplantation and Graft-Versus-Host Reaction

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Key words: allogeneic bone marrow transplantation, graft-versus-host reaction (disease) (GVHR (D)), graft-versus-leukemia (GVL), cytokines, adhesion molecules

Introduction

Graft-versus-host disease (GVHD) is one of the major complications based on the graft-versus-host reaction (GVHR) after allogeneic bone marrow transplantation. GVHR is mediated by immunocomponent cells, such as T and NK cells in the donor marrow, which recognize alloantigens of the host in an immunosuppressive state to be foreign and then attack. Although cellular immune responses are thought to be the principal mechanism for GVHR and GVHD (1), the involvement of cytokines in GVHD has been recently suggested by many researchers (2, 3), indicating that GVHR and GVHD are caused by various factors. An initial step of GVHR is the recognition of host alloantigens by donor T cells; nonspecific immune responses are generated thereafter. Both specific and nonspecific immune activation are involved in the induction of clinically established GVHD. GVHD consists of acute GVHD (aGVHD) and chronic GVHD (cGVHD), based on the time period (100 days) after bone marrow transplantation (4, 5).

Cellular immune responses and GVHR

It is well known that T cell depletion from donor bone marrow apparently reduces the incidence and the severity of GVHD, although this procedure increases the incidence of engraftment failure and leukemia relapse (6). This fact indicates that T cells play an important role in GVHD. However, early in 1980, it was reported that NK cells are also involved in the induction of GVHD. Transfer of T and NK cells into SCID mice enhanced GVHD (7). These findings supported the role of NK cells in GVHD.

T cells are related to the graft-versus-leukemia (GVL) effect. In particular, CD3+4−8− T cells include natural suppressor cells which inhibit GVHD but spare the GVL effect and IL-2 enhances the induction of natural suppressor cells (8).

Cytokines and GVHR

Regarding the role of cytokines in GVHD, administration of IL-1 receptor (R) antagonist reduces the severity of GVHD (9). IL-1 mRNA expression in peripheral blood mononuclear cells (PBMC) (3) and in the target tissues are increased in patients with GVHD. Serum IL-2 levels and IL-2 mRNA expression in PBMC were not increased in patients with GVHD (2, 3). In allogeneic bone marrow chimeras, IL-2 does not always enhance GVHD but rather it readily induces the induction of transplantation tolerance and enhances the engraftment when it is administered early after BMT (10). However, it is reported that IL-2 aggravates GVHD in murine allogeneic bone marrow chimeras. Soluble IL-2R in the sera is increased in patients with GVHD and administration of IL-2R ab inhibits GVHD, although the effect is transient (11). Therefore, the relationship between IL-2 and GVHD should be precisely analyzed.

Although it is reported that serum IL-6 levels are increased in GVHD (12), they are increased early after BMT and remain increased for a long time-period regardless of the presence or...
absence of GVHD. A subsequent increase of IFNγ and TNFα is often observed in patients with GVHD (2). Administration of anti-TNFα ab inhibits GVHD (13). Serum TNFα levels (14) and TNFα mRNA expression in PBMC are increased in patients with GVHD (3). These findings suggest that TNFα plays an important role in GVHD. However, it is reported that TNFα levels do not correlate well with GVHD. In our analysis of cytokines in patients with GVHD, TNFα as well as IL-6 alone did not induce GVHD (2). The interaction of IL-6, IFNγ, and TNFα was required for the induction of GVHD. Similar findings were observed in analysis of cytokine mRNA in PBMC (3).

**Immunosuppressive cytokines and GVHR**

Immunosuppressive cytokines can be produced during GVHD via the cytokine network in addition to immunostimulatory cytokines. In fact, analysis using a murine model with severe GVHD showed that IL-10 and TGFβ mRNA expression is decreased in spleen cells from allogeneic bone marrow chimeras with severe GVHD. Similar results were obtained in human allogeneic bone marrow transplants (15). Thus, GVHD appears to be induced by a cytokine imbalance between immunostimulatory cytokines and immunosuppressive cytokines.

**Cytokine receptor and GVHD**

It was reported that IL-1R antagonist (9) and anti-IL-2R ab inhibits GVHD (11). These findings suggest that the cytokine receptor expression and its function are important in GVHD. Even though some cytokine is overproduced, there is no use for the signal transduction if the cytokine receptor is not fully and functionally expressed. At least IL-2R and IL-6R mRNA expression are correlated with the severity of GVHD (16).

**Cytokine and cellular function**

Cytokines are involved in the expression of MHC and adhesion molecules in various cells. Therefore, these can affect the antigen recognition and subsequent activation of immunocompetent cells. Furthermore, cytokines can affect the production of other cytokines from other cells via the cytokine network. In addition to the effect on cytokine network, cytokines can affect cellular function such as vetcels and natural suppressor cells activated by IL-2, IL-3, IL-4, and IFNγ (17, 18). IFNγ, IL-1β, and TNFα stimulates macrophages, leading to the increased production of nitric oxide (19). The overproduction of nitric oxide can aggravate GVHD.

**T cell activation molecules and GVHR**

Adhesion molecules and T cell activation molecules can enhance the immune responses of immunocompetent cells (20). CD4, CD8, CD2, LFA1, ICAM1, CD28, and CTLA4 adhere to class II MHC, class I MHC, LFA3, ICAM1, LFA1, B7, and B70, respectively and enhance the immune responses. Anti-LFA1 and anti-ICAM1 antibodies inhibit the rejection of heart allograft in the rats. Recently, it was reported that GVHD is inhibited by CTLA4-Ig (21). Although the effect of CTLA4-Ig alone is very weak, the combination with other antibodies to adhesion molecules such as LFA1/ICAM1 appears to be more effective (22).

**Acute GVHD and chronic GVHD**

aGVHD is different from cGVHD in terms of the time-period of GVHD occurrence, clinical manifestations, and the target organs. Therefore, the mechanisms for aGVHD and cGVHD appears to differ from each other. Cytokine imbalance is similarly observed in both aGVHD and cGVHD. In the case of aGVHD, mature T cells contained in donor marrow directly attack the host tissues and various cytokines are produced, leading to cytokine imbalance. On the other hand, in the case of cGVHD, T precursor cells cannot be properly matured to permit self-nonself discrimination, leading to the generation of autoreactive T cells. These cells appears to be related to autoimmune-like disease. Furthermore, immunodeficiency, another characteristic feature in cGVHD, may be caused by the inappropriate interaction of T-B cell, functional deficiency in immunocompetent cells, suppressor cells, and immunosuppressive cytokines.

**Conclusion**

GVHR and GVHD after allogeneic BMT can be induced by the involvement of cellular immune responses and cytokine imbalance. These specific and nonspecific immune responses activate each other, leading to the clinically established GVHD. It is caused by not only one factor but several factors including cytokine receptor expression, MHC expression, and adhesion molecule expression which are intricately involved in the induction of GVHD. In the future, the separation of GVHD from GVL effect will be possible based on the analysis of GVHD and this procedure will be increasingly utilized in allogeneic bone marrow or peripheral blood stem cell transplantation.

**References**


3. Peripheral Blood Stem Cell Transplantation

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Key words: peripheral blood stem cells (PBSC), PBSC transplantation (PBSCT), autologous PBST, allogeneic PBSCT

Introduction

Peripheral blood stem cell transplantation (PBSCT) has been increasingly used as the third type of hematopoietic stem cell transplantation next to allogeneic and autologous bone marrow transplantation (allo-BMT and auto-BMT) in the treatment of hematologic malignancy and solid tumors (1). According to the latest nationwide survey by the Japan Society of Bone Marrow Transplantation, more than 500 transplants of PBSC have been performed since 1990.

Mobilization and collection of PBSC

Very small numbers of hematopoietic stem cells or progenitor cells circulate during steady-state hemopoiesis. These PBSC show a transient but marked increase during hematologic recovery from marrow-suppressive chemotherapy. This mobilization of PBSC from bone marrow into peripheral blood can be enhanced substantially when a hematopoietic growth factor such as granulocyte colony-stimulating factor (G-CSF) is administered during a recovery phase after chemotherapy (2, 3). Recent advances in the PBSC mobilization technique indicate that a sufficient number of PBSC for hematologic reconstitution after marrow-ablative therapy can be collected by leukapheresis using a continuous blood cell separator during hematologic recovery with or without hemopoietic growth factor (2, 4).

We investigated the effect of G-CSF on mobilization of PBSC in patients with leukemia or lymphoma based on a comparative study in a single patient (5). Two successive cycles of leukapheresis following cytotoxic chemotherapy were performed in 22 patients as follows: the first cycle was performed with cytotoxic mobilization in all patients while the second cycle was randomized into two groups: cytotoxic (n=10) and cytotoxic plus G-CSF (cytotoxic/G-CSF) (n=10) mobilization. Repetitive cytotoxic mobilization decreased the yields of myeloid (CFU-GM) and erythroid (BFU-E) progenitor cells. In contrast, cytotoxic/G-CSF mobilization produced significantly higher yields of CFU-GM (5.5 fold) and BFU-E (3.9 fold) than did cytotoxic mobilization alone (p<0.01). The ratio of CFU-GM to BFU-E was not affected by G-CSF. Furthermore, G-CSF led to an earlier peak of CFU-GM following chemotherapy. G-CSF is thus effective in expanding the pool of circulating...