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Review

Immune-Modulating Drugs and Hypomethylating Agents to Prevent or Treat Relapse after Allogeneic Stem Cell Transplantation

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A B S T R A C T

Allogeneic stem cell transplantation is a curative treatment option for many hematological diseases, and the numbers of transplantations are steadily increasing worldwide. Major progress has been made in lowering treatment-related mortality by reducing intensity of the conditioning regimen and by improving supportive care (eg, for infectious complications). Accordingly, relapse after allogeneic stem cell transplantation has become the major cause for treatment failure. Major efforts to prevent or treat relapse are focused on cellular- (T cell, natural killer cell), cytokine-, or antibody-based strategies to enhance the graft-versus-tumor effect or circumvent immunoescape. In the more recent years, new classes of agents have shown activity in several hematological malignancies, and besides their immediate antitumor activity, most of them also possess immune-modulatory qualities that may be useful alone or in combination with adoptive immunotherapy after allogeneic stem cell transplantation to enhance graft-versus-tumor effects. Here, we summarize the current knowledge and potential use of 2 of these compounds in preventing or treating relapse after allogeneic stem cell transplantation, namely immune-modulating drugs and hypomethylating agents.

INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) is an effective and curative treatment approach for hematological malignancies. The curative potential is mainly attributed to a strong graft-versus-leukemia (GvL) reaction mediated by allogeneic T lymphocytes and natural killer (NK) cells, which target leukemic recipient cells by distinct mechanisms. Donor lymphocyte infusion (DLI) after transplantation may augment the GvL effect and is, therefore, widely used to prevent or treat relapse after allo-SCT. However, DLI is associated with an increased risk of acute and chronic graft-versus-host disease (GvHD), and the majority of studies have shown a strong correlation between response to DLI and occurrence of GvHD. Furthermore, the effectiveness of DLI depends on the underlying disease, and responses differ substantially between relapsed chronic myeloid leukemia (>80%), multiple myeloma (30% to 40%), non-Hodgkin's lymphoma (40% to 50%), acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS) (15% to 30%), and acute lymphoblastic leukemia (10% to 20%) [1]. To reduce the risk of GvHD, CD8-depleted, CD4-enriched, or suicide gene–manipulated T cells have been investigated by several groups [2-6]. Generation of T cells specific for minor-histocompatibility antigens or tumor-specific antigens is under clinical evaluation [7-9]. To increase the efficacy of DLI, immunosuppression before DLI or combination with cytokine treatment (eg, interferon-α/GM-CSF or interleukin-2) can also be used [10-12]. New efforts are currently undertaken to boost GvL effect either by adoptive transfer of leukemia-specific T cells [13], or by post-transplantation vaccines [14]. Donor-derived NK cells exert GvL effect without causing GvHD [15], because NK cells are thought to specifically target host-antigen–presenting cells of hematopoietic origin, and, therefore, prevent the presentation of alloantigens to donor T cells. The antileukemic effect of NK cells may be best explained by predominant interaction of activating receptors such as killer immunoglobulin-like receptors (KIR) with the leukemic target cell [16-18]. Overall, despite the efficacy of cellular therapy, there is still need to improve results of adoptive cell therapy treatment after allo-SCT for reducing related complications such as GvHD as well as improving remission rate, duration, and risk of relapse.

In addition to the development of more specific and effective cell therapies, novel immune-modulatory drugs may be used as post-transplantation therapies alone or in combination with adoptive immunotherapy to augment GvL effects of allo-SCT and/or DLI. Ideally, a drug used as a single agent or in combination with adoptive immunotherapy should (1) exert additive antitumor effects either by increasing immunologically mediated graft-versus-tumor reactions and/or immediate anti-tumor mechanism; (2) have the capacity to reduce the risk of GvHD while maintaining the GvL effect; (3) show a favorable toxicity profile for early application after allo-SCT; and (4) be able to inhibit immunosuppressive and tolerance mechanisms in the host.

Here, we focus on the immune-modulatory properties of immune-modulating drugs (IMIDs) and hypomethylating agents that may be used after hematopoietic stem cell transplantation, either alone or in combination with adoptive immunotherapy, to augment GvL effects.

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IMMUNE-MODULATING DRUGS (IMIDS)

Immune-modulating drugs are thalidomide and its analogues, lenalidomide and pomalidomide. These drugs have an immediate antiproliferative effect on multiple myeloma, non-Hodgkin's lymphoma, and other hematological malignancies. In addition, antiangiogenic, anti-inflammatory, and immune-modulatory properties may contribute to antitumor effects; however, in vivo mechanisms mediating tumor responses remain to be elucidated. Thalidomide, a synthetic derivative of glutamic acid, which caused birth defects in the late 1950s and early 1960s, was the first IMID to be investigated with regard to its immune-modulating properties. The latter include antigen-independent stimulation of T cells and activation of NK cells [19]. It was later shown that second-generation IMIDs, such as lenalidomide and pomalidomide, are even more potent stimulators of T cell–mediated immunity [20].

Activation of T cells requires signaling through the T cell–receptor, for example provided by antigen-presenting cells (APC), in combination with costimulating signals. IMIDs stimulate only T cells that have been previously activated by APC, such as dendritic cells. This activation abrogates costimulation by APCs [21,22] and leads to a production of Th1-type cytokines (interleukin-2, interferon-γ) and a down-regulation of Th2-type cytokines (interleukin-4 and interleukin-10) [19]. T cell proliferation and cytokine production is significantly more amplified after stimulation with lenalidomide and pomalidomide compared with thalidomide; however, the clinical relevance of this finding remains to be determined. Molecular mechanisms mediating the IMID-induced proliferation and activation of T cells may involve transcriptional activity of activated protein-1 [23], increased tyrosine phosphorylation of CD28 on T cells [21,22], and activation of the PI3K-signaling pathway in activated T cells [21,22]. In vitro studies have shown that despite the increase of interleukin-2, generation of regulatory T cells is inhibited. However, in vivo data suggest an increase of FoxP3+ regulatory T cells after treatment with lenalidomide; however, this was interpreted as a counter-regulatory effect [24-26], as an increase of HLA-DR+ activated T cells preceded the increase of regulatory T cells [25].

IMIDs also stimulate the innate immune system, including γδ-T cells, NK cells, and NKT cells [20,21,27]. Lenalidomide increases dendritic cell–induced NKT cell expansion and secretion of interferon-gamma [28]. Thalidomide, lenalidomide, and pomalidomide increase NK cell proliferation in the presence of interleukin-2 [21], but only lenalidomide and pomalidomide enhance antibody-dependent cellular cytotoxicity, and natural cytotoxicity of NK cells [28,29]. The presence of cyclosporine A may abrogate IMID-induced NK cell cytotoxicity, suggesting interleukin-2-dependency of NK cell activation and proliferation [27]. Furthermore, in the presence of IMIDs, activated NK cells produce cytokines, such as monocyte chemotactic protein and granulocyte-macrophage colony stimulating factor, in response to antibody-coated target cells, which might attract tumor-specific T cells and dendritic cells [30].

Lenalidomide was tested in a dose-finding study after allo-SCT in multiple myeloma patients [31]. Lenalidomide was given between day 100 and day 180, and the maximal tolerable dose was 5 mg. Major toxicity was occurrence of acute GvHD, which was observed in 38% of the patients. Immune monitoring showed an early increase of γ-interferon–secreting CD4+ and C8+ T cells, which may explain the onset of GvHD. In addition, an increase of NK cell–mediated toxicity was seen, and the complete response rate increased from 24% to 42%. A correlation between response and NK cell and T cell activation was also noted. A similar incidence of GvHD has been observed by the HOVON group [32], which started lenalidomide at a dose of 10 mg 1 to 6 months after nonmyeloablative allo-SCT for multiple myeloma. They observed an increase of HLA-DR+ T cells, as well as of regulatory T cells, but without correlation to clinical outcome. In patients without complete remission after allo-SCT, the remission status improved in 37% of the patients after lenalidomide treatment, mainly by conversion from partial response to very good partial response or complete response.

Lenalidomide as salvage therapy in relapsed myeloma patients after allo-SCT induced an overall response rate of 66% including 8% CR with only mild grade I to II GvHD in 12% of the patients. In vivo measurement by flow cytometry showed significant increase of activated NK (NKp44) as well as T cells (CD3+HLA-DR+) [25].

Although all studies reported high remission rates of lenalidomide given after allo-SCT in myeloma patients, which could be even higher than after autologous stem cell transplantation [33], the effect of lenalidomide on GvHD remains controversial. Lenalidomide in combination with DLI was investigated in 12 myeloma patients who relapsed after allo-SCT. DLI was administered after 2 cycles of lenalidomide in an escalating mode, and no GvHD was seen [34]. In another study, lenalidomide was investigated as post-transplantation therapy in MDS or AML with del(5q)-abnormality. Lenalidomide (10 mg/day) was started at a median of 2.5 months after allo-SCT without dexamethasone. The study was stopped prematurely because 6 out of 10 patients developed acute GvHD grade III or IV [35]. In another trial, 16 myeloma patients who relapsed after allo-SCT received lenalidomide (25 mg/daily), either alone or in combination with dexamethasone, resulting in an overall response rate of 88%, and GvHD was seen only in patients who received lenalidomide without dexamethasone (5 of 13) [26]. These trials suggested that lenalidomide can cause acute GvHD if given early after transplantation, and the risk of GvHD is lower if the drug is given later or in combination with dexamethasone.

Thalidomide given with a median dose of 200 mg as salvage treatment for relapse after allo-SCT was investigated in 33 patients by the Société Française de Greffe et de Moelle et Thérapie Cellulaire. An objective response was seen in 29% of the patients, but 5 patients (15%) developed acute GvHD [36]. Low-dose thalidomide (100 mg), followed by DLI for progressive disease or residual disease after allo-SCT, was investigated in 18 patients with multiple myeloma post-allograft [37]. Only 2 patients developed mild GvHD, and the overall response was 67%, including 22% complete remissions. In summary, IMIDs have immune-stimulatory properties, which can be used effectively after allo-SCT, but because of the T cell–stimulating effect, the risk of inducing GvHD should be considered. (Table 1)

HYPOMETHYLATING AGENTS

Methylation plays a central role in epigenetic regulation of gene expression [38]. Cancer cells use hypermethylation to switch off a vast number of genes that are responsible for growth inhibition, differentiation, and apoptosis [39]. Further epigenetic modifications are used extensively in CD4 T cells to regulate linage commitment. DNA-methyltransferase-inhibitors azacytidine (AZA) or decitabine are