REVIEW

Relapsing Hematologic Malignancies after Haploidentical Hematopoietic Stem Cell Transplantation

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Haploidentical hematopoietic stem cell transplantation (HSCT) is a potentially curative therapeutic regimen that could increase donor availability to nearly 100%. Rapid advances in medical technology and the application of novel drugs mean that most haploidentical HSCT-associated complications can now be prevented or remarkably well controlled, even cured. However, relapsing hematologic malignancy remains a major cause of death in haploidentical HSCT recipients. Haploidentical HSCT should theoretically trigger a more potent graft-versus-tumor effect compared with human leukocyte antigen-identical transplantation, due mainly to the major histocompatibility complex and minor histocompatibility anitigen disparities on donors' immune cells and recipients' tumor cells. The underlying mechanisms of such relapsing hematologic malignancies remain elusive. In this review, we suggest correlating factors and potential mechanisms and examine feasible therapeutic and preventive strategies for relapsing hematologic malignancies after haploidentical HSCT.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative strategy for hematologic malignancies [1], solid malignancies [2], and other nonmalignant diseases [3]. This regimen has benefited patients since its emergence more than 50 years ago. In current clinical situations, a human leukocyte antigen (HLA)-matched HSCT is commonly the preferred type of transplantation, with HLA-matched sibling donors usually the first choice. For cases in which an HLA-matched related donor is not available, an HLA-matched unrelated donor is identified and selected through a donor registry. Clinical practice has demonstrated that only 50%-60% of HSCTs from HLA-matched donors are successful, with a much lower rate of success in patients of ethnic minorities [4]. With the aim of solving this conundrum and benefiting more patients, much effort has been expended in searching for feasible alternative approaches. Haploidentical HSCT appears to be a promising strategy, with a theoretically high donor availability of almost 100%. It also is less time-consuming than conventional HSCT, which requires a stringent matching process. Nevertheless, even after years of application, the high incidence of several critical complications, including severe graft-versus-host disease (GVHD), delayed engraftment, severe infection, and graft failure, still poses a barrier to the wider application of haploidentical HSCT to the benefit of more patients.

In recent years, based on surprising advances in transplantation and immunology, several attempts have been made to use T cell–depleted haploidentical bone marrow (BM) for the prevention of GVHD. The first ex vivo T cell–depleted haploidentical HSCTs using BM were performed in 4 children with immunodeficiency syndromes more than 20 years ago; all 4 patients were healthy at 12-15 months after discharge [5]. Since then, mega-doses of purified stem cells and T cell–depleted grafts have been used for haploidentical HSCT, and considerable progress has been made. Today, with 2 principle protocols—T cell

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depletion and T cell repletion—established worldwide, an encouraging survival rate of 20% has been achieved in patients with progressive hematologic malignancies [6]. Using this method, most complications can be prevented or remarkably well controlled, and in some cases even cured, due mainly to the application of advanced medical technologies and novel therapeutic drugs.

According to traditional immunobiological theory, haploidentical HSCT could be expected to trigger a more potent graft-versus-tumor (GVT) effect compared with HLA-identical transplants due to the major histocompatibility complex (MHC) and minor histocompatibility antigen (mHA) disparities on donor immune cells and recipient tumor cells, which might facilitate the repression of tumor relapse. In fact, a high risk of relapse after haploidentical T cell–depleted or T cell–replete HSCT has been documented in various hematologic malignancies, including acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome, multiple myeloma, chronic myelogenous leukemia, and lymphoma, under both myeloablative and nonmyeloablative (NMA) conditioning regimens, in both children and adults [7-13]. Studies performed within the past 5 years are summarized in Tables 1 and 2. These reports infer that relapsed hematologic malignancy after haploidentical HSCT is still the most common cause of death, although the specific incidence varies among reports, possibly due to the heterogeneity in patient series and diagnostic variations in the different cohorts. The mechanisms by which high-risk malignant cells survive under GVT effects remain elusive, however.

In our opinion, haploidentical HSCT has merit in improving survival probability, and haploidentical donors likely would be one of the main stem cell sources. In this review, we suggest correlating factors and potential mechanisms causing relapse of hematologic malignancies after haploidentical HSCT, then address the newly identified indications for relapse, as well as feasible therapeutic and preventive strategies.

POTENTIAL MECHANISMS FOR RELAPSING HEMATOLOGIC MALIGNANCIES AFTER HAPLOIDENTICAL HSCT

In ideal haploidentical HSCT, the initiating conditioning therapy, especially the myeloablative regimen, eradicates the majority of malignant hematologic cells. In addition, the posttransplantation GVT effects then eradicate any residual malignant cells remaining after conditioning therapy. Thus, in the case of in situ relapse, the residual malignant cells must survive ablation of the hematopoietic system, which includes malignant hematologic cells, and also survive the GVT reaction [38]. According to recent reports, malignant cell resistance to conditioning therapy demonstrated a similar process to that involved in drug resistance in chemotherapy [39-41], and certain factors might influence malignancy relapse, including, but not limited to, the cancerous microenvironment, cancer stem cells, gene polymorphisms, host ages, GVHD prevention strategies, disease status at transplantation, and gene mutations. Here we discuss corresponding factors and potential immune mechanisms involved in the emergence of relapsing malignancies after haploidentical HSCT (Figure 1).

Pretransplantation: Donor Selection Serves as an Initial Stage for Preventing Future Relapse

Maternal Tolerance Reduces GVT Potency Induced by Donor Transplants

Siblings, parents, and offspring are all potential haploidentical donors. Maternal tolerance and/or immunization should make consideration of maternal transplants a priority. The immune systems of mother and child are in close contact during pregnancy and achieve a delicate equilibrium, which might exert an influence on haploidentical transplantation later in life.

The maternal immune system, unlike that of the fetus, is mature and usually functional and thus is capable of being immunized by paternal histocompatibility antigens transmitted from the fetus. Antibodies directed against paternal HLA antigens [42] and memory type T lymphocytes directed against paternal major and minor histocompatibility antigens [43,44] are frequently found in multiparous women. Under such circumstances, humoral and cellular immunity against HLA and mHA in the offspring might mediate enhanced GVT effects after maternal donor transplantation. For patients undergoing T cell–depleted haploidentical HSCT, even though the majority of T cells have been removed, the small population of contaminant memory T cells transferred with the graft could still spontaneously undergo unopposed proliferation and play a vital role in the GVT process by virtue of the absence of pharmacologic GVHD prophylaxis [33]. Stern et al. [33] found relapse rates of 22.7% with maternal donors and 46.5% with paternal donors after T cell depletion in vitro excluding the sex effect, supporting the notion that the use of immunized maternal donors is associated with reduced relapse mortality with both T cell–depleted and T cell–replete HSCT. In contrast, for maternal donors who were not immunized but tolerized during pregnancy, low immune reactivity would weaken the recipient's GVT effect, contributing to the higher relapse rate than seen with immunized maternal donors.

The situation might be different when considering reciprocal transplantation, in which the mother is the recipient and the offspring is the donor. It is assumed