Biology of Blood and Marrow Transplantation 12:1169-1175 (2006)

1083-8791/06/1211-0001$32.00/0
doi:10.1016/j.bbmt.2006.07.001

Human Leukocyte Antigen DR15 Is Associated with Reduced Relapse Rate and Improved Survival after Human Leukocyte Antigen-Identical Sibling Hematopoietic Stem Cell Transplantation

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Received June 22, 2006; accepted July 6, 2006

ABSTRACT

Human leukocyte antigen (HLA) DR15 is associated with autoimmune cytopenia in patients with aplastic anemia, myelodysplastic syndrome, and paroxysmal nocturnal hemoglobinuria. Presence of this antigen also predicts response to immunosuppressive treatment. If DR15 expression on hematopoietic cells also favors induction of immune responses in an allogeneic setting, a lower relapse rate after hematopoietic stem cell transplantation (HSCT) might result through an enhanced graft-versus-leukemia effect. We retrospectively analyzed outcome of HLA-identical sibling HSCT in 192 consecutive patients with acute or chronic leukemia or non-Hodgkin lymphoma. Patients carrying the DR15 antigen had a higher estimated 5-year overall survival (76%) than did DR15-negative patients (55%; $P = .04$). Improved survival for DR15 patients was due to a significant decrease in death from relapse (5% for $DR15^+$ versus 24% for $DR15^-$; $P = .02$), whereas no difference was seen for rates of transplant-related mortality (19% and 21%, respectively; $P = .76$). Findings were confirmed by multivariate analyses. Our results show an association of DR15 with a decreased risk of disease relapse and improved survival after HSCT for leukemia or non-Hodgkin lymphoma. This adds to the growing list of links between DR15 and immune reactions in hematopoiesis.

KEY WORDS

Hematopoetic stem cell transplantation • Human leukocyte antigen • Graft-versus-host disease • Graft-versus-leukemia

INTRODUCTION

Autoimmune bone marrow hypoplasia and ensuing peripheral blood cytopenia are features of several different hematologic disorders, among them aplastic anemia (AA) and subgroups of myelodysplastic syndrome (MDS) and paroxysmal nocturnal hemoglobinuria. For AA, as for many other autoimmune disorders, an association to an HLA constellation, ie, the presence of the serologically defined DR2 antigen [1,2] and later its serologic DR15 split and genetic DRB1*15 allele counterpart [3], were identified. Further evidence for a role of DR15 in the pathogenesis of the disease comes from the fact that response rates to immunosuppressive therapy are higher in patients expressing the DR15 antigen than in those who do not [4-6]. Recent studies in patients with MDS and paroxysmal nocturnal hemoglobinuria—2 diseases intricately related to AA, with subgroups presenting a clinical picture difficult to distinguish from AA—have confirmed DR15 as a marker of susceptibility for the disease and for response to immunosuppressive treatment [5,7,8]. This association of DR15 with autoimmune cytopenia raises the possibility that the DR15 molecule preferentially presents an autoantigen on hematopoietic precursor cells evoking an immune reaction and eventually causing bone marrow aplasia. High antibody titers to a candidate autoantigen pre-

sented by DR15 have recently been described in patients with AA or MDS [9].

T lymphocyte-mediated graft-versus-leukemia reaction after allogeneic hematopoietic stem cell transplantation (HSCT) offers a unique setting to study immunologic effects against hematopoietic precursor cells. Several retrospective studies that assessed the influence of HLA antigens on outcome after HSCT have found rates of acute graft-versus-host disease (aGVHD) being altered by HLA antigens, but no effect has been reported in rates of relapse or overall survival [10,11]. A recent report looking specifically for an effect of DR15 described a decreased incidence of GVHD in patients expressing the DR15 antigen compared with those who do not, showing that presence of DR15 might influence donor-versus-recipient alloreactivity after HSCT [12].

We hypothesized that, if the DR15 antigen confers a preferential susceptibility to T cell-mediated (auto-)immunity, an increased alloimmune effect might be seen after HSCT, resulting in a lower relapse rate after HSCT for patients carrying the DR15 antigen. We therefore analyzed the outcome of patients treated with allogeneic HLA-identical sibling HSCT for malignant hematopoietic disorders with respect to presence or absence of the DR15 antigen.

METHODS

Study Design

In a single-center cohort study, we retrospectively analyzed overall mortality, causes of death, and incidence/severity of aGVHD and chronic GVHD (cGVHD) after T cell-replete HLA-identical sibling transplantation in 192 consecutive patients who underwent transplantation between 1989 and 2004 for acute myeloid and lymphoblastic leukemias, chronic myeloid leukemia, and chronic lymphocytic leukemia/non-Hodgkin lymphoma. All patients had undergone HLA-DRB1 molecular typing. Outcome of patients expressing the DR15 antigen was compared with that of patients negative for DR15.

HLA Typing

Patients and their donors were HLA typed at the National Reference Laboratory for Histocompatibility (Geneva, Switzerland) or in the Hematology Laboratory of the University Hospital (Basel, Switzerland). DRB1* typing by polymerase chain reaction sequence-specific primer or polymerase chain reaction sequence-specific oligonucleotide probe hybridization using commercially available reagents was performed in all patients.

Patients

Patient characteristics according to DR15 status are presented in Table 1. No significant differences were seen between patients positive or negative for the DR15 antigen.

Approximately 50% of patients underwent transplantation for acute leukemia, and the other 50% had chronic myeloid leukemia or chronic lymphocytic leukemia/non-Hodgkin lymphoma. Disease stage was defined as early in the following circumstances: acute leukemia in first remission or chronic myeloid leukemia in chronic phase. All other disease stages were classified as advanced. Patients with acute myeloid or lymphoid leukemia were additionally stratified according to cytogenetical abnormalities, identified by conventional cytogenetics or molecular testing for fusion transcripts: for acute myeloid leukemia, the presence of t(15;17), t(8;21), or inv(16) was considered as conferring a low risk of relapse; deletions involving the short arm of chromosome 5 or 7, inv(3), and complex abnormalities were considered as high risk; patients with normal karyotype or carrying any other translocation were considered at intermediate risk [13]. For acute lymphoblastic leukemia, the translocations t(9;22), t(4;11), and t(1;19) were considered high risk; presence of a hyperdiploid karyotype or of the translocation t(12;21) were considered low risk; other translocations or a normal karyotype were considered intermediate risk [14].

All patients received T lymphocyte-replete grafts. Peripheral blood was the stem cell source in 66% of patients. Conditioning consisted of cyclophosphamide and total body irradiation (12 Gy) with or without VP16 in most patients. Conditioning was myeloablative except for patients treated with fludarabine and single-dose total body irradiation (2 Gy). GVHD prophylaxis after transplantation consisted of cyclosporin A with or without methotrexate except for patients receiving nonmyeloablative conditioning, where cyclosporin A plus mycophenolate mofetil was administered instead.

Controls

Two German cohorts [15,16] and 1 Swiss cohort [17] of healthy individuals (routine blood donors) served as controls for estimation of the frequency of HLA-DR15 in the region of origin of our patients.

Endpoints and Definitions

Endpoints were overall survival, disease-related mortality (DRM), which was defined as death from relapse/disease progression after transplantation, and transplant-related mortality (TRM), which was defined as death from any nonrelapse cause after transplantation. Incidence and severity of aGVHD and cGVHD were secondary endpoints and graded according to established criteria [18].