Case Report

GMSMJ

Greater Mekong Subregion Medical Journal

Sequential Conditioning Un-manipulated Haploidentical Hematopoietic Stem Cell Transplantation in A Patient with High Risk and Refractory Acute Myeloid Leukemia by Using A Second-degree Relative Donor

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Received 8 August 2022 • Revised 20 August 2022 • Accepted 31 August 2022 • Published 1 January 2023

Abstract:

Following the second course of induction chemotherapy, only 10 to 20 percent of patients with relapsed/refractory acute myeloid leukemia can achieve complete remission. We reported the case of a patient with high-risk, refractory acute myeloid leukemia who underwent sequential conditioning T cell-replete haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide from a second-degree relative donor. The sequential conditioning regimen consisted of thiotepa 5 mg/kg on days -15 and -14, etoposide 100 mg/m^2 on day-13 to -10, cyclophosphamide 400 mg/m^2 on day-13 to -10, and mesna on day-13 to -10, followed by fludarabine 30 mg/m^2 on day-6 to -2, and melphalan 140 mg/m^2 on day-2. The graft-versus-host disease prophylaxis regimen consisted of cyclophosphamide, tacrolimus, and mycophenolate mofetil. Neutrophil and platelet engraftment occurred on day +15 and +32. On day+56, the patient developed CMV reactivation, which was successfully treated with ganciclovir. The last follow-up was on day +300; the patient remained in complete remission. He had mild chronic graft-versus-host disease of the oral mucosa, mild anemia, and mild thrombocytopenia. This patient demonstrated that sequential conditioning T cell- replete haploidentical hematopoietic stem cell transplantation utilizing a second-degree relative donor is feasible and may be a promising therapy option for patients with relapsed/refractory acute myeloid leukemia.

Keywords: Refractory acute myeloid leukemia, Sequential conditioning, Hematopoietic stem cell transplantation

Introduction

Over the past decade, advances in genetic and molecular studies that provide new insights into how acute myeloid leukemia (AML) develops and is regulated by complex molecular pathways have led to the development of more effective treatments. These include chemotherapy, targeted therapy, and allogeneic hematopoietic cell transplantation. Even though these therapeutic techniques have the potential to cure AML, the 5-year survival rate for individuals aged up to 60 years is still approximately 50 percent, while it ranges from 5 percent to 15 percent for those older than 60 years.[1-3] In addition, the prognosis for patients with relapsed/refractory acute

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GMSMJ 2023; 3 (1): 23-30

myeloid leukemia remains dismal. Only 10 to 20 percent of patients can achieve a complete response following the second course of induction chemotherapy.[4-8] After allogeneic stem cell transplantation under normal conditioning regimen, the range of overall survival for relapsed/refractory acute myeloid leukemia patients is 19-33 percent.[9-10]

The Munich group has developed sequential conditioning regimens consisting of adding a brief course of antileukemia chemotherapy prior to reduced-intensity conditioning hematopoietic stem cell transplantation. The combination of fludarabine, amsacrine, and cytarabine (FLAMSA), followed by cyclophosphamide, 4 Gy of total body irradiation, or busulfan (FLAM SA-BuCy), and anti-thymocyte globulin (ATG) is one of the first and most effective strategies reported, with a 2-year leukemia-free survival rate of 37 percent and an overall survival rate of 40 percent.[11] Various groups have further developed the concept of sequential conditioning regimens. Compared to the original FLAMSA, the antileukemia chemotherapy and pre-transplantation phases of the sequential conditioning regimens have been modified, resulting in increased intensity. In relapsed/refractory myeloid malignancies, protocols such as TEC (thiotepa, etoposide, cyclophosphamide) or clofarabine-based strategies have been reported to have a comparable overall survival rate of 30 percent to 45 percent.[12-18]

In the absence of a matched sibling or unrelated donor, allogeneic stem cell transplantation utilizing other donors is widely utilized.[19] Recently, the use of high-dose post-transplant cyclophosphamide has made it possible to evaluate the potential of selecting first-degree relatives (brother, sister, father, mother, son, or daughter) as haploidentical donors for allogeneic stem cell transplantation. Interestingly, treatment of post-transplant cyclophosphamide decreases the incidence of severe acute/chronic graft-versus-host disease due to the early elimination of alloreactive T cells.[20] Unfortunately, some patients may not have a suitable related donor due to factors such as the parents' advanced age and the absence of siblings or children. The statistical probability of having a haploidentical donor among siblings is fifty percent; however, it approaches one hundred percent when both biological parents and offspring are considered. When considering the kid of a matched or haploidentical sibling as a potential donor, the percentages of the donor and receiver being haploidentical stay at 50 percent and 25 percent, respectively. Thus, second-degree relatives (nephew, niece, uncle, aunt) may be considered a source of stem cell grafts.[20,21] Herein, we describe a patient with high risk and refractory acute myeloid leukemia who underwent a T-replete haploidentical allogeneic stem cell transplantation with post-transplant cyclophosphamide from a second-degree relative donor.

Case presentation

A 56-year-old Thai man presented to the dermatology department with multiple erythematous non-blanchable macules on the tip of his second toe, between his fourth and fifth toes, on the lateral malleolus, and on the lateral side of his left foot, as well as an indurated erythematous plaque on his left elbow that had been tender for one week. The dermatologist selected the left elbow for a punch biopsy. According to the pathology report, there was an epidermal ulcer accompanied by lymphocytic vasculitis. Aside from the rash, he was in good health.

A complete blood count revealed anemia with a reverse neutrophil/lymphocyte ratio; hemoglobin 11.8 g/dL; hematocrit 33.9%; white blood cell counts 5.49 x 10^9/L; neutrophil 12.9%; lymphocyte 64%; monocyte 21%; eosinophil 0.9 %; and platelet 211 x 10^9/L. The patient was referred to the

hematology department for further investigation.

Physical examination revealed mildly pale conjunctivae, no icteric sclerae, no hepatosplenomegaly, and no lymph node enlargement. A bone marrow biopsy revealed sufficient hypercellular (80-100 percent) packed bone marrow with diffuse leukemic infiltrate characterized by pleomorphic blasts with medium to large, round to slightly ovoid nuclei, homogeneously dispersed to condense chromatin, inconspicuous nucleoli, and occasional indented nuclei with scanty cytoplasm. Flow cytometric analysis of bone marrow demonstrated CD13 (+), CD15 (-), CD33 (+), CD34 (+), CD64 (+), CD11 (-), HLA-DR (+), MPO (+) compatible with acute myelomonocytic leukemia. Chromosomal analysis from bone marrow showed 46, XY, del (8) (q13q24.1), add (14) (q32), del (13) (q12q32). After complete investigations, this patient was diagnosed with acute myeloid leukemia at high risk due to a complex karyotype.

He underwent standard induction chemotherapy for acute myeloid leukemia consisting of idarubicin for three days and cytosine arabinoside (Ara-c) for seven days. On day 8, he developed a progressive confluent bright erythematous rash on his lower back, both arms, and forearms; multiple erythematous non-blanchable macules on both thighs and both legs; and dry lips but no genuine mucosal involvement as manifestations of early Steven Johnson syndrome; therefore, drug allergy to allopurinol or cytosine arabinoside was the most likely cause. We did not performed genetic testing for HLA-B* 58:01 due to leukopenia, but we decided to switch from allopurinol to febuxostat.

The presence of blast cells on the peripheral blood smear on day 28 prompted us to assess therapy response. A bone marrow biopsy revealed inadequate hypocellular bone marrow with increased residual leukemic blasts (18–28 percent), finely scattered chromatin, inconspicuous nucleoli, and sparse to abundant cytoplasm consistent with acute myeloid leukemia. In addition, bone marrow flow cytometric analysis identified a large population of CD11b (+), CD13 (+), CD15 (+), CD33 (+), CD34 (+), CD64 (+), HLA-DR (+), MPO (+), whereas chromosomal analysis revealed 46, XY. In Thailand, salvage treatment options for acute myeloid leukemia include 1) re-induction with a 7+3 regimen, but the patient might develop severe allergic reaction to Ara-c, 2) hypomethylating agent, but the remission rate for the treatment with hypomethylating agent alone is very low, 3) intense salvage chemotherapy such as the FLAG/idarubicin regimen, but we are concerned about serious complications such as infections due to prolonged neutropenia, and 4) sequential conditioning T cell-replete haploidentical hematopoietic stem cell transplantation that was developed by the Munich group, combining an intensive conventional anti-leukemic regimen with a reduced intensity conditioning regimen, which we hope that this procedure will provide not only a direct cytotoxic effect from chemotherapy but also a strong graft-versus-leukemia effect. After discussing treatment options with the patient, he decided to undergo a sequential conditioning regimen for hematopoietic stem cell transplantation.

We selected his nephew, a 32-year-old male, as the donor for sequential conditioning T cell-replete haploidentical hematopoietic stem cell transplantation because the patient was childless and had just one 60-year-old haploidentical sister. Both the recipient and donor had an O blood group, Rh positive, and a positive CMV serology. Antibodies against donor-specific antigens were not detected in the patient. Because amsacrine is unavailable in Thailand, we adapted the prototype FLAMSA-based sequential conditioning regimen into the Thio-ETO-Cy-Flu-Mel

regimen. This regimen includes of thiotepa 5 mg/kg on day -15 and -14, etoposide 100 mg/m^2 on day-13 to -10, cyclophosphamide 400 mg/m^2 on day-13 to -10, and mesna on day-13 to -10, followed by fludarabine 30 mg/m^2 on day-6 to -2, and melphalan 140 mg/m^2 on day-2. Graft-versus-host disease prophylaxis regimen consists of cyclophosphamide, tacrolimus, and mycophenolate mofetil administered post-transplant. Acyclovir and voriconazole were given at a prophylactic dose. Peripheral blood stem cells were infused on day 0 at a dose of 10 x 10^6/kg of the recipient.

Neutrophil and platelet engraftment occurred as early as day +15 and day +32, respectively, with full-donor whole-blood (WB) chimerism occurring on day +31. (Engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count higher than 0.5 x 10^9 /L, sustained > 20 x 10^9/L platelets, and hemoglobin > 8 g/dL, free of transfusion requirements.[22] A bone marrow biopsy done on day +27 revealed adequate hypocellular bone marrow (20-40 percent) with substantially enhanced developing myeloid precursors and considerably reduced maturing erythroid precursors and megakaryocytes. There was no residual leukemia detected. Flow cytometric analysis of bone marrow also revealed negative results for minimal residual disease, and chromosomal analysis revealed 46, XY. The patient had no signs and symptoms of acute graft-versus-host disease.

On day +32, he was diagnosed with cytomegalovirus reactivation (CMV viral load 3,420 copies/ml, log 3.53); he was treated as an outpatient with valganciclovir. Before administration of valganciclovir, a complete blood count revealed the following: hemoglobin 10.3 g/dL, hematocrit 30.2%, white blood cell counts 5.31 x 10^9/L, neutrophil 56.2%, lymphocyte 18.2%, monocyte 10.0%, eosinophil 2.0%, and platelet 101 x 10^9/L. On day +56, he was admitted due to high fever and watery diarrhea as the cytomegalovirus viral load increased (CMV viral load 18000 copies/ml, log 4.25). The complete blood count revealed the following: hemoglobin 10.2 g/dL, hematocrit 29.7%, white blood cell counts 10.65 x 10^9/L, neutrophil 52%, lymphocyte 24%, eosinophil 24 %, and platelet 79 x 10^9/L. Differential diagnoses included bacterial infection, CMV colitis, and acute graft-versus-host disease. He received an intravenous antibiotic and ganciclovir treatment. Due to the patient's refusal to have a colonoscopy, oral budesonide was administered to treat acute graft-versus-host disease. A few days later, the fever and diarrhea had subsided.

On day +80, there was no detectable CMV viral load, but the patient developed pancytopenia. In order to rule out a relapse of acute myeloid leukemia, a bone marrow biopsy was performed and revealed significantly hypocellular (5-10 percent) bone marrow with diminished maturing trilineage hematopoiesis. There was no residual leukemia detected. Also negative for the minimal residual disease was the flow cytometric examination of bone marrow. Given that pancytopenia might be a consequence of ganciclovir, the patient was administered eltrombopag, and the dosage was reduced when pancytopenia improved.

On day +200, a repeat bone marrow biopsy and flow cytometric analysis revealed mild hypocellularity and the absence of minimal residual disease. Day+300 was the last follow-up. The patient's health was excellent. He had mild oral mucosal chronic graft-versus-host disease, mild anemia, and mild thrombocytopenia.

Discussion

This 56-year-old Thai man, presented with anemia, a reverse neutrophil/lymphocyte ratio, and cutaneous vasculitis. Investigations concluded with a diagnosis of acute myeloid leukemia with a high risk due to complex

karyotypes. He received standard induction chemotherapy (7+3) and developed Steven Johnson syndrome in its early stages, most likely due to Ara-c. Even though chromosomal tests revealed a normal karyotype, he had a significant number of residual leukemic cells in his bone marrow. Following a discussion with the patient, we considered treatment with sequential conditioning T cell-replete haploidentical hematopoietic stem cell transplantation, as prior studies have shown that patients who failed to achieve a complete remission with initial therapy are associated with 10–20 percent complete remission rates following the second course of induction chemotherapy. In addition, prognostic factors include cytogenetics, age, and the failure of a prior salvage treatment.[4,5,22]

The pioneering study developed by the Munich group has sequential conditioning regimens consisting of adding a brief course of antileukemia chemotherapy prior to reduced-intensity conditioning hematopoietic stem cell transplantation. With fludarabine, amsacrine, and cytarabine (FLAMSA), followed by cyclophosphamide, 4 Gy of total body irradiation, or busulfan (FLAM SA-BuCy), and anti-thymocyte globulin (ATG), remission was described in 66 of 75 patients (88%) with a median age of 52.3 years. With a median follow-up period of 35.1 months (range: 13.6 to 47.6 months), the overall and leukemia-free survival rates at 2 years were 42% and 40%, respectively.[11] Various groups have further developed the concept of sequential conditioning regimens.[12,14,15,17,18] Another group developed a novel sequential method that combined chemotherapy with broad anticancer activity (thiotepa 10 mg/kg, etoposide 400 mg/m^2, and cyclophosphamide 1600 mg/m^2 from day-15 to day-10) with a reduced-intensity conditioning regimen (fludarabine 150 mg/m^2, i.v. busulfan 6.4 mg/kg, and thymoglobulin 5 mg/kg from day-6 to day-2. In cases involving haploidentical donors, cyclophosphamide was added post-transplant. This retrospective multicenter analysis comprised 72 patients (median age, 54 years) with refractory hematologic malignancy (44 with acute myeloid leukemia, 7 with acute lymphoblastic leukemia, 15 with myelodysplastic syndrome/myeloproliferative neoplasms, and 6 with lymphomas). With a median follow-up of 21 months, the 2-year overall survival (OS) and event-free survival (EFS) for recipients of haploidentical donors were 54.7% and 49.3%, respectively.[23] In a recent study published by the Acute Leukemia Working Party of the EBMT to evaluate transplantation outcomes following six types of the sequential conditioning regimen for patients with relapsed/refractory acute myeloid leukemia undergoing allogeneic hematopoietic stem cell transplantation, the Flu-Mel-TBI8 group demonstrated the best leukemia-free survival in patients younger than 55 years of age.[13] According to these studies, since amsacrine is unavailable in Thailand, we adjusted the sequential conditioning protocol into the Thio-ETO-Cy-Flu-Mel protocol. Based on the Thio-ETO-Cy-Flu-Bu protocol proposed by Dulery R. et al.[24], we changed the conditioning regimen component from Flu-Bu to Flu-Mel due to higher survival and decreased non-relapse mortality demonstrated in several studies.[25-27] Surprisingly, early engraftment of neutrophils occurred on day+15 in the absence of severe infection and acute graft-versus-host disease.

Regarding donor selection, since the patient was childless and had only a 60-year-old sister, we selected his 30-year-old nephew to be the donor. To our knowledge, there is a study that uses collateral-related donor for haploidentical hematopoietic stem cell transplantation using ATG as a graft-versus-host disease prophylaxis regimen, and another study reported 3 patients who received a T-replete haploidentical allogeneic stem cell transplantation with post-transplant

cyclophosphamide from their second-degree relative nephews.[22,28]

Importantly, our results suggest that using a second-degree relative as a haploidentical donor should not be a constraint from a matching perspective, hence increasing the likelihood of finding a donor for a particular patient. Conversely, some collateral-related haploidentical donors may be less available or eager to donate than first-degree haploidentical donors and hesitate to do so. The recent evidence that the use of a haploidentical donor who is unrelated is possible may aid in resolving this issue. Our findings also indicated that we might be on the verge of eliminating the critical HLA barrier. In addition, combining solid organ transplantation with allogeneic hematopoietic stem cell transplantation from the same haploidentical donor might eliminate immunosuppression drugs in this circumstance because stable tolerance may be developed, as previously reported for kidney transplantation.

Conclusion

The author demonstrates that sequential conditioning T-replete haploidentical hematopoietic stem cell transplantation with high-dose post-transplant cyclophosphamide using a second-degree relative donor is feasible, allowing for complete engraftment and mild acute and chronic graft-versus-host disease in a patient with refractory acute myeloid leukemia and a high blast count. Regarding the number of mismatched HLA antigens on the non-shared haplotype, the number of mismatched HLA antigens on the second-degree relative donor does not appear to negatively influence sequential conditioning T-cell replete haploidentical transplantation with post-transplant cyclophosphamide.

Conflict of interest

The author has declared no conflict of interest

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