Transpl Int (1997) 10: 328–330

BRIEF REPORT

Heiwa Kanamori
Shin Sasaki
Etsuko Yamazaki
Seiji Ueda
Michiko Hattori
Hitoshi Fukawa
Tomohiko Tamura
Hiroshi Harano
Michio Matsuzaki
Kouji Ogawa
Hiroshi Mohri
Takao Okubo

Eradication of minimal residual disease during graft-versus-host reaction induced by abrupt discontinuation of immunosuppression following bone marrow transplantation in a patient with Ph[1]-ALL

Received: 28 January 1997
Received after revision: 4 April 1997
Accepted: 15 April 1997

H. Kanamori (✉) · S. Sasaki
E. Yamazaki · S. Ueda · T. Tamura
H. Harano · K. Ogawa · H. Mohri
T. Okubo
First Department of Internal Medicine,
Yokohama City University School of Medicine,
3–9 Kukuura, Kanazawa-ku,
Yokohama 236, Japan
Fax: + 81 45 786 3444

M. Hattori · H. Fukawa
Division of Internal Medicine,
Yokohama Ekisaikai Hospital,
Yokohama, Japan

M. Matsuzaki
Division of Blood Transfusion,
Yokohama City University Hospital,
Yokohama, Japan

Abstract We observed a patient in whom graft-versus-host disease (GVHD) appeared to induce a positive effect. This 32-year-old male with Philadelphia chromosome-positive acute lymphoblastic leukemia received a bone marrow transplant (BMT) from an HLA-identical sibling donor. We analyzed the bone marrow with the reverse transcriptase-polymerase chain reaction to screen for the minor bcr/abl transcript, which indicates the presence of minimal residual disease (MRD). MRD was present in the pre-and post-transplant phases. There was no evidence of acute GVHD by post-transplant day 45. We abruptly discontinued the immunosuppressive therapy in an attempt to eliminate MRD by inducing an antileukemic reaction during GVHD. GVHD associated with diarrhea and liver dysfunction developed on day 64. On day 105, MRD disappeared and GVHD was treated with prednisolone and cyclosporin. The disappearance of MRD may have been due to the graft-versus-leukemia (GVL) effect mediated by the alloimmune response of donor T lymphocytes. These findings suggest that induction of the GVL effect may be useful for eliminating MRD after BMT in leukemia patients at high risk of recurrence of the disease.

Key words Acute lymphoblastic leukemia, minimal residual disease, GVHD · Residual disease, GVHD, acute lymphoblastic leukemia · GVHD, acute lymphoblastic leukemia, minimal residual disease

Introduction

In patients with leukemia who undergo bone marrow transplantation (BMT), the risk of relapse is 20%–60%, depending on the disease status at the time of BMT [6]. The major cause of relapse is the presence of minimal residual disease (MRD) that has not responded to myeloablative regimen and/or to the immune response after transplantation [8]. Patients with leukemic relapses after BMT are treated with conventional chemotherapy, a second BMT, interferon, and/or donor lymphocyte transfusion (DLT). Induction of the graft-versus-leukemia (GVL) effect [3] following DLT is a useful strategy in patients with chronic myelogenous leukemia (CML) who relapse after BMT [5].

Although the mechanism of the GVL effect is poorly understood, its effectiveness in patients with subclinical relapses suggests that it may be useful for eliminating post-transplant MRD. The GVL effect usually occurs concomitantly with graft-versus-host disease (GVHD) [15]. Experimental findings suggest that the GVL effect may be blocked by cyclosporin A [16]. We induced the GVL effect by abruptly discontinuing immunosuppressive therapy in an attempt to eradicate MRD in a leukemia patient who underwent BMT.

Case report

A 32-year-old man with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^1-ALL) who was in remission was admitted to our hospital for BMT on 18 September 1995. He had been treated with L-asparaginase, vincristine, and prednisolone. After achieving a complete remission, he received a consolidation regimen including cytosine arabinoside and mitoxantorone, and four courses of intrathecal methotrexate therapy to protect against meningeal leukemia. Cytogenetic analysis of bone marrow showed normal male metaphases, but the reverse transcriptase-polymerase chain reaction (RT-PCR) revealed the presence of the bcr/abl transcript.

The patient received an allogeneic BMT from his HLA-identical brother on 11 October 1995. The pretransplant conditioning regimen consisted of fractionated total body irradiation (day −9 to −6; 3 Gy/day), thiotepa (days −5 and −4; 210 mg/m^2 per day), and cyclophosphamide (days −3 and −2; 2250 mg/m^2 per day). He also received a GVHD prophylactic regimen consisting of methotrexate (day 1, 15 mg/m^2 per day and days 3 and 6, 10 mg/m^2 per day) and cyclosporin (3 mg/kg per day by continuous infusion). He received 250 μg/day of granulocyte colony-stimulating factor by continuous infusion beginning on day 1 to aid in granulocyte recovery. His granulocyte count was above 1000/μl on day 16 and his platelet count was about 3×10^4/μl on day 19. On day 28, a bone marrow aspirate was hypocellular with no leukemic cells, although cytogenetic analysis showed normal male metaphases. RT-PCR of bone marrow showed persistence of MRD on days 28 and 63. Because the patient had no evidence of acute GVHD, immunosuppressive therapy with cyclosporin was abruptly discontinued on day 45 to induce the GVL effect in an attempt to eradicate MRD by the antileukemic effect. The patient complained of diarrhea with abdominal pain on day 64. The volume of watery diarrhea increased to 1700 ml/day on day 92. Liver dysfunction was observed on day 61, and his SGOT and SGPT levels increased to 98 and 218 U/l, respectively. These clinical and laboratory findings were consistent with acute GVHD, despite the absence of skin lesions. Cyclosporin was again administered beginning on day 75 to control acute GVHD. The diarrhea did not improve and the serum aminotransferase levels were twice the normal upper limit. Therefore, prednisolone was added to the drug regimen.

On day 105, a bone marrow aspirate revealed hematologic and cytogenetic remissions with the disappearance of MRD. Peripheral blood mononuclear cells were analyzed by fluorescence-activated cell sorting with monoclonal antibodies. As expected, the population of NK cells increased after the discontinuation of cyclosporin. The number of T cells increased from 1247/μl on day 29 to 2655/μl on day 110. The population of CD57 + /CD8 + cells increased from 427/μl to 1218/μl.

The immunosuppressive therapy was tapered after the improvement in GVHD. The patient remains in hematologic remission without MRD at 10 months post-transplantation.

Discussion

Patients with Ph^1-ALL have a high risk of mortality and are treated with BMT to prolong survival. BMT effectively eradicates leukemic cells in patients with acute myeloblastic leukemia, ALL, and CML. However, leukemic relapse after BMT remains a major problem [6] and has been attributed to the presence of MRD. PCR [10] has been used to detect MRD after BMT and chemotherapy. The residual presence of the bcr/abl transcripts is correlated with clinical relapses in patients with Ph^1-ALL [7].

In the present case, the discontinuation of cyclosporin induced the antileukemic effects resulting in the elimination of MRD, as confirmed by the results of RT-PCR. We believe that the disappearance of MRD in the present case resulted from the discontinuation of immunosuppressive therapy, although spontaneous remission of lymphoid neoplasia has been observed in patients who relapse after BMT [9, 12].

Collins et al. [1] reported that two patients who had relapses after allogeneic BMT achieved complete remissions following the discontinuation of immunosuppressive therapy. In one patient, the GVL effect was associated with acute GVHD; the other patient achieved hematologic and cytogenetic remission before clinical GVHD developed. Those authors suggested that T cells may have mediated the GVL effect in the second patient. Higano et al. [2] reported that a complete remission was achieved following discontinuation of cyclosporin in a patient with acute myeloblastic leukemia who relapsed following allogeneic BMT. The GVL effect was associated with active chronic GVHD, which was well controlled with corticosteroids. Peterson et al. reported that discontinuation of cyclosporin was effective in a patient with Burkitt's lymphoma who relapsed after allogeneic BMT, although the reinstitution of immunosuppressive therapy for GVHD was associated with a recurrence of the lymphoma [11].

The percentage and the number of NK cells increased significantly after the discontinuation of immunosuppressive therapy in the present case, suggesting that the increased population of T cells, including cytotoxic T cells and NK cells, may have been a mechanism of the GVL effect , although we did not analyze lymphokine-activated killer cells and cytokines. Jiang et al. reported that the presence of cytotoxic T cells reacting with host leukemic cells was correlated with the GVL effect and GVHD [4].

The mechanism underlying the GVL effect in BMT patients is unknown. Kolb et al. have suggested that the use of DLT as adoptive immunotherapy induces the GVL effect in patients with CML who relapse after BMT, and that the GVL effect may result from a cytotoxic T-cell response to leukemia-specific antigens or minor antigens [5]. Slavin et al. have reported long-term observations of the first patient with remission reinduced by allogeneic cell therapy using donor peripheral blood lymphocytes [13]. Interestingly, they insist that DLT is effective in ALL, in contrast to Kolb et al., who report that DLT is ineffective in ALL [13, 14]. Although DLT is a promising strategy for leukemia patients who relapse, careful monitoring of patients for severe myelosuppression and prompt treatment of GVHD are essential.

The abrupt discontinuation of immunosuppressive therapy following BMT may not induce a stronger immune reaction against leukemic cells than DLT. However, the adverse reaction caused by discontinuation of immunosuppressive therapy can be controlled with medication, and this approach may be more successful for eliminating leukemic cells in patients with a low tumor burden, such as those with MRD after BMT, especially in patients at high risk of relapse.

References

1. Collins RH Jr, Rogers ZR, Bennett M, Kumar V, Nikein A, Fay JW (1992) Hematologic relapse of chronic myelogenous leukemia following allogeneic bone marrow transplantation: apparent graft-versus leukemia effect following abrupt discontinuation of immunosuppression. Bone Marrow Transplant 10: 391–395
2. Higano CS, Brixey M, Bryant EM, Durnam DM, Doney K, Sullivan KM, Singer JW (1990) Durable complete remission of acute nonlymphocytic leukemia associated with discontinuation of immunosuppression following relapse after allogeneic bone marrow transplantation. A case report of a probable graft-versus-leukemia effect. Transplantation 50: 175–177
3. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, Rimm AA, Ringden O, Rozman C, Speck B, Truitt RT, Zwaan FE, Bortin MM (1990) Graft-versus-leukemia reactions after bone marrow transplantation. Blood 75: 555–562
4. Jiang YZ, Kanfer EJ, Macdonald D, Cullis JO, Goldman JM, Barrett AJ (1991) Graft-versus-leukemia following allogeneic bone marrow transplantation: emergence of cytotoxic T lymphocytes reacting to host leukemia cells. Bone Marrow Transplant 8: 253–258
5. Kolb HJ, Schattenberg A, Goldman JM, Hertenstein B, Jacobsen N, Arcese W, Ljungman P, Ferrant A, Verdonck L, Niederwieder D, Rhee F, Mittermueller J, Witte T, Holler E, Ansari H (1995) Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood 86: 2041–2050
6. Kumar L (1994) Leukemia: management of relapse after allogeneic bone marrow transplantation. J Clin Oncol 12: 1710–1717
7. Miyamura K, Morishima Y, Tanimoto M, Saito H, Kojima S, Kodera Y, Mizutani S (1990) Prediction of clinical relapse after bone marrow transplantation by PCR for Philadelphia-positive acute lymphoblastic leukemia. Lancet II: 890
8. Miyamura K, Barrett AJ, Kodera Y, Saito H (1994) Minimal residual disease after bone marrow transplantation for chronic myelogenous leukemia and implications for graft-versus-leukemia effect: a review of recent results. Bone Marrow Transplant 14: 201–209
9. Odom LF, August CS, Githens JH, Humbert JR, Morse H, Peakman D, Sharma B, Rusnak SL, Johnson FB (1978) Remission of relapsed leukemia during a graft-versus-host reaction: a "graft-versus leukemia reaction" in man ? Lancet II: 537–540
10. Okamoto R, Harano H, Matsuzaki M, Motomura S, Maruta A, Kodama F, Mohri H, Okubo T (1995) Predicting relapse of chronic myelogenous leukemia after allogeneic bone marrow transplantation by bcr-abl mRNA and DNA fingerprinting. Am J Clin Pathol 104: 510–516
11. Peterson FB, Appelbaum FR, Bigelow CL, Buckner CD, Clift RA, Sanders JE, Storb R, Sullivan KM, Weiden PL, Fefer A, Thomas ED (1989) High-dose cytosine arabinoside, total body irradiation and marrow transplantation for advanced malignant lymphoma. Bone Marrow Transplant 4: 483–488
12. Singer JW, Keating A, Ramberg R, McGuffin R, Sanders JE, Sale G, Fialkow PJ, Thomas ED (1983) Long-term stable hematopoietic chimerism following marrow transplantation for acute lymphoblastic leukemia: a case report with in vitro marow culture studies. Blood 62: 869–872
13. Slavin S, Naparstek E, Nagler A, Ackerstein A, Kapelushnik J, Or R (1995) Allogeneic cell therapy for relapsed leukemia after bone marrow transplantation with donor peripheral blood lymphocytes. Exp Hematol 23: 1553–1562
14. Slavin S, Naparstek E, Nagler A, Ackerstein A, Samuel S, Kapelushnik J, Brautbar C, Or R (1996) Allogeneic cell therapy with donor peripheral blood cells and recombinant human interleukin-2 to treat leukemia relapse after allogeneic bone marrow transplantation. Blood 87: 2195–2204
15. Sullivan KM, Weiden PL, Storb R, Witherspoon RP, Feter A, Fisher L, Buckner CD, Anasetti C, Appelbaum FR, Badger C, Beatty P, Bensinger W, Berenson R, Bigelow C, Cheever MA, Clift R, Deeg HJ, Doney K, Greenberg P, Hansen JA, Hill R, Loughran T, Martin P, Neiman P, Petersen FB, Sanders J, Singer J, Stewart P, Thomas ED (1989) Influence of acute and chronic graft-versus-host disease on relapse and survival after bone marrow transplantation from HLA-identical siblings as treatment of acute and chronic leukemia. Blood 73: 1720–1728
16. Weiss L, Reich S, Slavin S (1990) Effect of cyclosporine A and methylprednisolone on the GVL effect across major histocompatibility barriers in mice following allogeneic bone marrow transplantation. Bone Marrow Transplant 6: 229–233