CASE REPORT

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Successful treatment of B-cell lymphoma associated with hemophagocytic syndrome using autologous peripheral blood CD34 positive cell transplantation followed by induction of autologous graft-versus-host disease

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Abstract  A 56-year-old man who presented with persistent high fever and abdominal pain was diagnosed as having a B-cell lymphoma associated with hemophagocytic syndrome (B-LAHS). As post-remission therapy, the patient was treated with high-dose chemotherapy followed by infusion of autologous CD34+ cells that had been isolated from the peripheral blood buffy coat. Cyclosporin and interferon (IFN)-γ were administered to induce autologous graft-versus-host disease (GVHD). Hematopoietic recovery promptly occurred and skin GVHD developed on day 26 after CD34+ cell transplantation. The patient has been in complete remission without therapy for 20 months since transplant. Autologous CD34+ cell transplantation in combination with induction of autologous GVHD may be efficacious in obtaining a cure for B-LAHS.

Key words B-cell lymphoma · Hemophagocytic syndrome · CD34-selection · PBSCT · Autologous GVHD

Introduction

Hemophagocytic syndrome (HPS) is a clinicopathological entity characterized by fever, hepatosplenomegaly, liver dysfunction, pancytopenia, and proliferation of histiocytes with erythrophagocytosis [17]. This syndrome has been observed during the clinical course of a wide variety of disorders, including infections and malignancies. Although most lymphoid malignancies associated with HPS are of T-cell origin [3], some cases of HPS occur in association with B-cell lymphoma [11, 14]. B-cell lymphoma associated with HPS (B-LAHS) has an acute and fatal course, since it tends to spread into extranodal sites such as the bone marrow, liver, spleen, or lung from the early stage of its clinical course without peripheral lymphadenopathy. Although some chemotherapeutic agents such as doxorubicin and cyclophosphamide (CY) have an anti-tumor activity, combination chemotherapy for B-LAHS using these agents is usually unsuccessful. To our knowledge, only one treatment success reported for B-LAHS, which was achieved with conventional chemotherapy [11], resulted in recurrence of the disease (personal communications). We report the first case of B-LAHS successfully treated with high-dose chemoradiotherapy in combination with an infusion of autologous purified CD34+ peripheral blood (PB) progenitor cells followed by induction of autologous graft-versus-host disease (auto-GVHD) using cyclosporin (CyA) and interferon (IFN)-γ.

Case report

A 56-year-old Japanese man presented with high fever, anorexia, and abdominal pain that had lasted for 4 weeks. Physical examination revealed a temperature of 39.2°C and tender enlargement of the liver and spleen. There was no peripheral lymphadenopathy. A blood count showed a hemoglobin concentration of 11.1 g/dl, a platelet count of 74 × 10^9/l, and a white blood cell (WBC) count of 5.7 × 10^9/l, with 1.1 × 10^9/l of large atypical cells that had abundant basophilic cytoplasm often containing fine vacuoles, multilobulated nuclei, and distinct nucleoli. Azurophilic granules were absent in the cytoplasm of the large atypical cells. Bone marrow (BM) examination revealed an infiltration of the large atypical cells that constituted 36.8% of the nucleated cells and were all negative for peroxidase activity.
Increased histiocytes constituting 3.2% of the nucleated cell showed phagocytosis of red blood cells, erythroblasts, WBCs, platelets, and the large atypical cells. BM biopsy also demonstrated clusters of neoplastic cells that were positive for CD20 but not for CD45RO in immunohistology of formalin-fixed paraffin sections. Pathological diagnosis was diffuse, large B-cell lymphoma. In situ hybridization of the patient’s BM cells using an autoradiographic probe for the highly transcribed Epstein-Barr virus (EBV)-encoded small nuclear RNA (EBER-1) sequence revealed the absence of EBV-RNA in the cells. Cytogenetic analysis of marrow cells showed such a complicated abnormality as follows: 49, Y, inv(3)(q11q21), der(3)(q11q27), add(4)(q21), der(7)(p15), add(8)(p11), add(9)(p24), add(14)(q27), +mar1, +mar2, in 4 cells; 49, ideim, +Y; t(13;19)(p22;q25), add(7)(p22), -mar1, in 1 cell; 49, ideim, +Y; +del(5)(q31), +9, -add(9), +21, -mar1, -mar2, in 1 cell; 52, ideim, +inv(X)(p11q13), +5, +11, +12 -mar2, in 2 cells; 46, XY, in 6 cells. BM mononuclear cells (MC), isolated using Ficol/Hypaque (Pharmacia, Uppsala, Sweden) gradient centrifugation were CD2–, CD3–, CD5–, CD10–, CD16–, CD19+, CD20+, CD34–, CD56–, CD24–, and human leukocyte antigen (HLA)-matched with fluoro-activated cell sorting (FACS) analysis (Becton Dickinson, Mountain View, Calif.; CD56, Coulter; the other monoclonal antibodies, Becton Dickinson, Mountain View, Calif.). A level of biochemical profile included a serum albumin level of 2.7 g/dl, a bilirubin level of 0.9 mg/dl, an alkaline phosphatase level of 1567 U/I, a r-glutamyl transpeptidase level of 303 U/I, a lactate dehydrogenase level of 4272 U/I, an aspartate amino-transferase level of 305 U/I, an alanine amino-transferase level of 194 U/I, and a ferritin level of 4867 ng/ml.

Ultrasonography of the patient’s abdomen confirmed hepatosplenomegaly with no focal lesions. Blood cultures were negative. Hepatitis B viral surface antigen and an antibody to hepatitis C virus were not detected in the serum. Serologic testing detected no evidence of recent infections by herpes simplex virus, cytomegalovirus, toxoplasma, hepatitis A, syphilis, human T-lymphotropic virus (HTLV)-1, or human immunodeficiency virus (HIV)-1. The EBV serology included an anti-viral capsid antibody (VCA) immunoglobulin (Ig) G-antibody titer of 1:160, an anti-VCA IgM-antibody titer of <1:10, an anti-early antigen IgG-antibody titer of <1:10, and an anti-Epstein-Barr nuclear antigen antibody titer of 1:20, indicative of past infection. Southern blot analysis of BMMCs showed the gene of the Ig heavy chain [7] to be in a clonal rearrangement, while those of both T-cell receptor (TCR) / and / chains [1] to be in the germ-line configuration. Based on these findings, B-LAHS was diagnosed.

Five courses of the CHOP regimen (CY, vincristine, doxorubicin, prednisolone) resolved the patient’s clinical symptoms and produced hematologic remission. Post-remission therapy with hematopoietic stem cell transplantation was planned in view of poor prognosis of B-LAHS in the literature. There was no HLA-matched donor in the patient’s family. PB stem cells were mobilized with granulocyte colony-stimulating factor (G-CSF; filgrastim 5 μg/kg/day) following the fifth course of CHOP and collected by leukapheresis using the Cobe Spectra Cell Separator (Cobe Laboratories, Lakewood, Colo.). PB CD34+ cells were positively immunoselected using the Baxter Isolex Magnetic Cell Separation System (Isolex 50, Baxter Immunotherapy, Irvine, Calif.) and cryopreserved at −80°C until use. The preparative regimen included fractionated total body irradiation (FTBI, 2.0 Gy × 6) and CY, 50 mg/kg/day for 2 days. The PB CD34+ cells (a total dose of 1.3 × 10⁸/kg; a CD34 purity, 98%) were infused into the patient 4 months after the diagnosis. To induce auto-GVHD, the patient received CyA 2.5 mg/kg/day i.v. for 21 days starting at day 1, and IFN-γ 50 μg/week s.c. from day 7 through day 28 after transplant [10, 12]. G-CSF was started on day 1 to accelerate neutrophil recovery. The patient showed prompt hematologic recovery. The neutrophil count exceeded 0.5 × 10⁹/l at 11 days, and platelet count was 50 × 10⁹/l 25 days following transplantation. On day 26 after transplantation, an erythematous maculopapular rash affecting the trunk, extremities, and palms developed. This was clinically suggestive of grade-II acute GVHD. A skin biopsy obtained from the forearm showed an upper dermal mononuclear cell infiltrate extending into the epidermis with microabscess and cytoplasm body formation and epidermal basal layer degeneration, which were consistent with the diagnosis of GVHD. The rash resolved spontaneously in a week after the onset. Diarrhea or liver function abnormalities did not develop. The patient has been in complete remission without therapy for 30 months since transplantation.

Discussion

In recent years, some trials have demonstrated a significantly higher survival rate in patients with poor-prognosis non-Hodgkin’s lymphoma after high-dose chemoradiotherapy with autologous blood progenitor cell support than after conventional chemotherapy, although others have not found a difference between them [2, 7, 15, 16]. Regarding patients with aggressive B-cell lymphoma, there is a report that showed significant survival benefits for those treated with autologous BM transplantation compared with those treated with the methotrexate, doxorubicin, cyclophosphamide, prednisone, bleomycin (MACOP-B) regimen [4]. Maximum doses of chemotherapy and total body irradiation have been defined to avoid therapy-related mortality. However, despite the use of such high-dose regimens, the relapse rate for non-Hodgkin’s lymphoma following autologous blood cell transplantation remains in excess of 40% [15]. The report that a patient with B-cell lymphoma developed fatal B-LAHS following auto-vascular blood stem cell transplantation (PBST) [17] suggests that this therapeutic modality may be insufficient for eradication of neoplastic B cells. We therefore employed two methods to effectively prevent relapse of B-LAHS in our patient after PBST. The first was purging of malignant clonogenic cells from the autograft using a positive selection of CD34+ cells [5], and the second was an induction of auto-GVHD [6, 10].

In the patients with malignant lymphoma, the rate of relapse after autologous hematopoietic stem cell transplantation seems higher than that after allogeneic stem cell transplantation. The high relapse rate in autografted patients is thought to be in part due to the absence of GVHD, since most GVHD is potentially accompanied by a graft-versus-tumor (GVT) effect [8]. Induction of auto-GVHD following auto-PBST is reported to be able to generate a GVT effect, which offers one avenue of hope for decreasing the relapse rate in patients with hematologic malignancies [6, 10]. Of our series of 19 patients with malignant lymphoma who received CyA and IFN-γ following auto-PBST in the same way the present patient did, 12 (63%) have developed auto-GVHD. This was pathologically proven (data not shown). In all of the 12 patients, we could demonstrate the existence of autoreactive T cells at the active stage of autologous