Brief report

Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab

Stuart L. Goldberg, Andrew L. Pecora, Robert S. Alter, Mark S. Kroll, Scott D. Rowley, Stanley E. Waintraub, Kavita Imrit, and Robert A. Preti

Efforts to reduce relapse of non-Hodgkin lymphoma after autologous transplantation have included ex vivo stem cell selection and/or peritransplantation immunotherapy. The late infectious and immunologic consequences of these maneuvers are not well understood, although an increase in early cytomegaloviral disease after CD34$^+$ stem cell selection and an alteration in immunoglobulin and T-cell recovery after peritransplantation rituximab has been noted. We report the first 2 cases of progressive multifocal leukoencephalopathy caused by JC papovavirus after autologous peripheral blood stem cell transplantation and a case each of cytomegalovirus retinitis and pneumonitis. All 4 patients experienced significant impairment of CD4 T-cell recovery, placing them at risk for these unusual viral infections. The clustering of cases is concerning because all occurred shortly after the introduction of peritransplantation rituximab into treatment protocols (4 of 62 immunotherapy recipients compared with 0 of 276 without; $z = 3.595$; $P < .001$), although a direct association with this CD20 B-cell–directed therapy remains speculative. (Blood. 2002;99:1486-1488)

Introduction

Immune reconstitution after autologous stem cell transplantation may be delayed by ex vivo cellular manipulations and/or peritransplantation immunotherapies. Although an increase in early viral infections, including cytomegaloviral (CMV) disease, has been noted after CD34-selected autografting, little is known about the late infectious consequences of stem cell selection.[1-3] Rituximab (Genentech, South San Francisco, CA; IDEC Pharmaceuticals, San Diego, CA), a monoclonal antibody directed against CD20$^+$ cells, is being investigated as an in vivo purging agent before stem cell collection and may have a role in the treatment of minimal residual disease after transplantation.[4] The immunologic effects and infectious complications related to rituximab in the peritransplantation setting, or even when used in conjunction with standard dose chemotherapy, also remain unclear.

We recently observed 2 cases of progressive multifocal leukoencephalopathy and a case each of CMV retinitis and pneumonitis occurring in lymphoma patients 9, 20, 5, and 12 months after undergoing autologous peripheral blood stem cell (PBSC) transplantation. These cases represent our first experiences with JC papovavirus after transplantation and CMV retinitis/pneumonitis postautologous transplantation. All occurred after the introduction of peritransplantation rituximab into our treatment protocols. Since 1991 we have treated 338 adult lymphoma patients with a conditioning regimen consisting of high-dose carmustine 600 mg/m^2, etoposide 1600 mg/m^2, cytarabine 24 g/m^2, and cyclophosphamide 90 mg/kg (BVAC). The 4 cases of viral infection occurred among the 62 patients receiving peritransplantation rituximab (6.4%) compared with no cases among the 276 not receiving immunotherapy ($z = 3.595$; $P < .001$).

Study design

A 34-year-old woman presented in January 1999 with stage IIB mediastinal thymic B-cell non-Hodgkin lymphoma. She was treated with CHOP (cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone) chemotherapy and consolidative radiotherapy. In October 1999 she experienced a widespread relapse that involved the lungs, pericardium, bone, spleen, kidneys, liver, and adrenal glands. She received debulking chemotherapy with one cycle of DICE (dexamethasone, ifosfamide, carboplatin, and etoposide) and one cycle of DICEP (dose-intensive cyclophosphamide, etoposide, and cisplatin). In December 1999 she received high-dose chemotherapy with BVAC rescued by an infusion of 3.62×10^6 CD34 cells/kg unmanipulated, cryopreserved autologous PBSCs. Hematopoietic engraftment, facilitated by filgrastim, with a neutrophil count above 500/μL occurred on day 21 after transplantation. Subsequently, she received 4 weekly cycles of rituximab 375 mg/m^2. In August 2000 (9 months after transplantation), while still in remission, she developed right upper-extremity weakness. Evaluation for thromboembolic disease was negative. Over the next several months her neurologic status deteriorated with the development of a right hemiparesis, ataxia, and dysarthria. Magnetic resonance imaging in late September 2000 revealed areas of white matter disease consistent with a demyelinating process. Polymerase chain reaction analysis of spinal fluid in October 2000 confirmed JC viral DNA. She was HIV negative. Her total lymphocyte count was 216/μL with 89/μL CD4$^+$ and 41/μL CD8$^+$ cells. Peripheral B cells included decreased CD19$^+$ (4/μL) and CD20$^+$ cells (4/μL) as well as CD56$^+$ cells (97/μL). Quantitative serum immunoglobulins revealed an immunoglobulin (Ig)G of 627 mg/dL, IgA 58 mg/dL, and IgM 19 mg/dL. Despite treatment with continuous infusion interleukin 2 and intermittent cidovir she died in March 2001.

A 42-year-old woman presented in January 1992 with a stage III marginal zone non-Hodgkin lymphoma. She received CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy and entered remission.

From the Adult Blood and Marrow Transplantation Program, Hackensack University Medical Center, NJ; Centra State Medical Center, Freehold, NJ; and Progenitor Cell Therapy, Hackensack, NJ.

Submitted June 26, 2001; accepted October 5, 2001.

Reprints: Stuart L. Goldberg, 20 Prospect Ave, Suite 400, Hackensack, NJ 07601; e-mail: sgoldberg@humed.com.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 U.S.C. section 1734.

Her first relapse in December 1995 responded again to CVP, which was changed to C-MOPP (cyclophosphamide, mechlorethamine, vincristine, procarbazine, and prednisone) in June 1996. A second relapse in a para-aortic node in August 1998 was treated with 2 cycles of DICE and concurrent rituximab 375 mg/m^2. In January 1999 she underwent high-dose chemotherapy with BVAC and was rescued with 0.91×10^6/kg CD34 selected (Isolex 300i, Nexell Therapeutics, Irvine, CA) autologous PBSCs. Neutrophil recovery facilitated by filgrastim occurred on day 11. She received 2 additional cycles of rituximab during the second posttransplantation month. Her posttransplantation course was complicated by cyclophosphamide-induced cardiomyopathy in April 1999, *Clostridium difficile* colitis in September 1999, and varicella zoster dermal infection in March 2000. In August 2000 (20 months after transplantation), while still in complete remission, she noted visual changes and right-sided ataxia. Magnetic resonance imaging confirmed white matter disease and polymerase chain reaction of the spinal fluid revealed JC viral DNA. Laboratory studies in October 2000 revealed depressed quantitative immunoglobulins with an IgG of 163 mg/dL, IgA of 17 mg/dL, and IgM 2 of mg/dL. Peripheral blood analysis in December 2000 revealed lymphocytosis (3934/μL), but depressed CD4$^+$ (551/μL) with elevated CD8$^+$ (2596/μL) and normal CD19$^+$ (315/μL) and CD20$^+$ (315/μL) counts. HIV serologies were negative. Without therapy she has made slow recovery, although she remains with significant muscular weakness and left visual field defects. Immunologic studies in June 2001 (30 months after transplantation) continued to reveal low CD4$^+$ (462/μL) and elevated CD8$^+$ (1437/μL) cells with IgG of 866 mg/dL.

A 42-year-old man with diffuse large cell, B-cell non-Hodgkin lymphoma stage IIB involving Waldeyer ring received CHOP plus consolidative radiotherapy. Four years later he experienced a left supraclavicular relapse that responded to DICE salvage therapy. Subsequently, he underwent BVAC autologous CD34 selected (2.91×10^6 cells/kg) PBSC transplantation. Neutrophil engraftment occurred on day 13. He received 2 cycles of rituximab before and 2 cycles after transplantation. His posttransplantation course was complicated by bischloroethylnitrosourea pneumonitis requiring steroid therapy. In May 2000 (5 months after transplantation and 2 months into steroid therapy) he noted visual changes. Ophthalmologic evaluation revealed CMV retinitis. He was lymphopenic (1200/μL) with a CD4 count of 12/μL and CD8 count of 420/μL, suppressed IgG 365 mg/dL, IgM 29 mg/dL, and low-normal IgA 70 mg/dL. HIV serologies were negative.

A 66-year-old man with diffuse large cell, B cell non-Hodgkin lymphoma stage IVB achieved a partial response to 6 cycles of CHOP chemotherapy. He received rituximab 375 mg/m^2 twice followed by DICE salvage therapy. Subsequently, in February 1999 he underwent BVAC autologous PBSC transplantation (2.62×10^6 CD34 cells/kg unmanipulated) and achieved neutrophil engraftment on day 20. Six months after transplantation he developed a perirectal abscess with varicella zoster, requiring prolonged antiviral therapy. Ten months after transplantation he developed profound thrombocytopenia. Staging studies failed to demonstrate lymphoma recurrence, and bone marrow immunophenotyping revealed 7% lymphoid cells with 0% CD19, 1% CD20, 21% CD4, and 6% CD8 cells. The thrombocytopenia was subsequently refractory to prednisone 1 mg/kg, intravenous immunoglobulin, azathioprine, and staph A column, and during treatment (1 year after transplantation) he developed dyspnea and confusion and suddenly died. At autopsy he was found to have CMV pneumonitis and multiple cerebral hemorrhages.

Approval for these studies was obtained from the Hackensack University Medical Center's institutional review board. Informed consent was provided according to the Declaration of Helsinki.

Results and discussion

Progressive multifocal leukoencephalopathy (PML) is an uncommon demyelinating disease of the central nervous system caused by JC papovavirus. Primary JC viral infection during childhood, which occurs in 75% of the population, results in lifelong viral latency in the kidneys and B-cell lymphocytes.[5] Clinical disease is hypothesized to occur when infected B cells become activated during periods of immunosuppression and subsequently enter the brain, where astrocytes and oligodendrocytes support JC virus replication that result in neurologic damage.[6] Inflammatory responses to the JC virus by T cells within PML lesions are associated with transient stabilization of symptoms.[7] Death within 6 months is common. JC viral reactivation is typically observed among patients with severe immunodeficiency states such as a general impairment of Th1-type T-helper function.[8] In the HIV population, PML is strongly correlated with depressed CD4$^+$ lymphocyte counts.[9] Rare cases of PML have been reported among patients with lymphoma.[10-12] Although urinary excretion of the related BK polyomavirus is common after blood and marrow transplantation, less than 10 cases of PML have been noted after allogeneic bone marrow transplantation,[13,14] autologous bone marrow transplantation,[15-18] and autologous purged marrow transplantation.[19] Our cases represent the first reports after autologous PBSC transplantation.

CMV is a well-described infection among allogeneic transplantation recipients and individuals with T-cell deficiencies. Although viral reactivation occurs with similar frequencies after allogeneic and autologous transplantation, clinical disease occurs in only 2% to 8% of autologous marrow recipients.[20,21] A comparative study noted an increased odds ratio of 17.0 of CMV disease among recipients of CD34-selected peripheral blood stem cells (7 of 31 patients) versus recipients of unselected peripheral blood stem cell support (10 of 237 patients).[3] Clinical disease after hematopoietic stem cell transplantation typically involves a pattern of early (first 3 months) pneumonitis and enteritis (including all 17 patients in the above study) rather than retinitis that is more common among patients with HIV disease and severe T-cell deficiencies.[22]

The failure of our patients to obtain late immunologic reconstitution after autologous PBSC transplantation in the absence of relapse or other clinical problems is unusual. T-cell CD3$^+$ repopulation typically occurs by 2 to 4 months. Low CD4/CD8 ratios, related to both low numbers of CD4$^+$ and elevated CD8$^+$ with low levels of naive CD4$^+$ CD45RA cells may exist during the first 6 months but return to baseline by 1 year. T-cell function, as measured by mitogen studies and mixed lymphocyte reactions, returns to baseline by 1 year.[23] Even the introduction of CD34$^+$ selection techniques to reduce potential tumor contamination does not greatly influence long-term immunologic reconstitution after PBSC infusions, with no significant differences in the kinetics of CD4$^+$, CD8$^+$, CD45RA$^+$, and CD45RO$^+$ cells.[24,25] CD19$^+$ B-cell numbers return to baseline within 3 months, but in vivo function measured by immunoglobulin levels typically requires more than 6 months after both selected and unselected infusions.

CD20, the target of rituximab, is expressed on virtually all mature peripheral blood and lymphoid tissue B cells, but not by resting or activated T cells, monocytes, or granulocytes; thus, T-cell recovery in the setting of peritransplantation rituximab might be suspected to be unaffected.[26] However, preliminary studies have suggested delayed immune reconstitution with the combination of rituximab and CD34-selected transplantation. Among recipients of CD34-selected, B-cell antibody–purged stem cell infusions receiving posttransplantation rituximab, decreased IgG levels were noted in 10 of 20 patients at 6 months and 6 of 11 at 1 year. T-cell recovery was also impaired with CD4 counts less than 200/μL observed in 12 of 20 patients at 6 months and in 4 of 11 at 1 year.[27] A second study of CD34-selected autographs with pretransplantation rituximab noted 5 of 13 patients with T-helper counts less than 200/μL at 6 months, and 8 of 8 CMV-seropositive patients developing reactivation CMV-DNA in blood at least once after transplantation.[28] Our cases of PML and CMV disease suggest that the addition of peritransplantation rituximab, which results in delayed T-cell reconstitution after autografting, may have serious consequences for late clinical infectious disease.

References

1. Miyamoto T, Gondo H, Miyoshi Y, et al. Early viral complications following CD34-selected autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. Br J Haematol. 1998;100:348-350.
2. Sica S, Salutari P, Orto La Barbera E, Sora F, Piccirillo N, Leone G. Infectious complications after CD34-selected autologous peripheral blood stem cell transplantation. Br J Haematol. 1998;101: 592-593.
3. Holmberg LA, Boeckh M, Hooper H, et al. Increased incidence of cytomegalovirus disease after autologous CD34-selected peripheral blood stem cell transplantation. Blood. 1999;94:4029-4035.
4. Goldberg SL, Pecora AL, Jennis AA, Preti RA, Moss TJ. Rituximab permits in-vivo purging and collection of tumor free stem cell products prior to autologous transplantation for B-cell non-Hodgkin's lymphoma [abstract]. Blood. 1999;94: 618a.
5. Shaw KV. Polymaviruses. In: Fields BN, Knipe DM, Howley PM, eds. Fields Virology. 3rd ed. Vol 2. Philadelphia, PA: Lippincott-Raven; 1996: 2027-2043.
6. Major EO, Amemiya K, Tormatore CS, Houff SA, Berger JR. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. Clin Microbiol Rev. 1992;5:49-73.
7. Hair LS, Nuovo G, Powers JM, Sisti MB, Britton CB, Miller JR. Progressive multifocal leukoencephalopathy in patients with human immunodeficiency virus. Hum Pathol. 1992;23:663-667.
8. Weber F, Goldmann C, Kramer M, et al. Cellular and humoral immune response in progressive multifocal leukoencephalopathy. Ann Neurol. 2001;49:636-642.
9. Fong IW, Toma E. The natural history of progressive multifocal leukoencephalopathy in patients with AIDS. Canadian PML Study Group. Clin Infect Dis. 1995;2:1305-1310.
10. Bjerrum OW, Hansen OE. Progressive multifocal leukoencephalopathy in Hodgkin's disease. Scand J Haematol. 1985;34:442-445.
11. Colosimo C, Lebon P, Martelli M, et al. Alpha interferon therapy in a case of probable progressive multifocal leukoencephalopathy. Acta Neurol Belg. 1992;92:24-29.
12. Anders KH, Becker PS, Holden JK, et al., Multifocal necrotizing leukoencephalopathy with pontine predilection in immunosuppressed patients: a clinicopathological review of 16 cases. Hum Pathol. 1993;24:897-904.
13. O'Shaughnessy K, Goldman JM, Roddie M, et al. Dizziness and confusion after bone marrow transplantation. Br Med J. 1994:309:262-265.
14. Owen RG, Pathmore RD, Smith GM, et al. Cytomegalovirus-induced T-cell proliferation and the development of progressive multifocal leukoencephalopathy following bone marrow transplantation. Br J Haematol. 1995;89:196-198.
15. Mesquita R, Parravicini C, Bjorkholm M, et al. Macrophage association of polyomavirus in progressive multifocal leukoencephalopathy: an immunohistochemical and ultrastructural study. Case report. APMIS. 1992;89:196-198.
16. Seong D, Bruner JM, Lee KH, et al. Progressive multifocal leukoencephalopathy after autologous bone marrow transplantation in a patient with chronic myelogenous leukemia. Clin Infect Dis. 1996;23:402-403.
17. Przepiorka D, Jaeckle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. Bone Marrow Transplant. 1997;20:983-987.
18. Re D, Bamborschke S, Feiden W, et al. Progressive multifocal leukoencephalopathy after autologous bone marrow transplantation and alpha-interferon. Bone Marrow Transplant. 1999;23: 295-298.
19. Coppo P, Laporte JP, Aoudjhane M, et al. Progressive multifocal leucoencephalopathy with peripheral demyelinating neuropathy after autologous bone marrow transplantation for acute myeloblastic leukemia (FAB5). Bone Marrow Transplant. 1999;23:401-403.
20. Wingard JR, Chen DYH, Burns WH, et al. Cytomegalovirus infection after autologous bone marrow transplantation with comparison to infection after allogeneic bone marrow transplantation. Blood. 1988;71:1432-1437.
21. Hebart H, Schroder A, Loffler J, et al. Cytomegalovirus monitoring by polymerase chain reaction of whole blood samples from patients undergoing autologous bone marrow or peripheral blood progenitor cell transplantation. J Infect Dis. 1997; 175:1490-1493.
22. Coskuncan NM, Jabs DA, Dunn JP, et al. The eye in bone marrow transplantation, VI: Retinal complications. Arch Opthalmol. 1994;112:372-379.
23. Steingrimsdottir H, Gruber A, Bjorkholm M, Svensson A, Hansson M. Immune reconstitution after autologous hematopoietic stem cell transplantation in relation to underlying disease, type of high-dose therapy and infectious complications. Haematologica. 2000;85:832-838.
24. Laurenti L, Sica S, Sora F, Piccirillo N, et al. Long-term immune recovery after $CD34^+$ immunoselected and unselected peripheral blood progenitor cell transplantation: a case-control study. Haematologica. 1999;84:1100-1103.
25. Nachbaur D, Kropshofer G, Heitger A, et al. Phenotypic and functional lymphocyte recovery after $CD34^+$ enriched versus non-T cell depleted autologous peripheral blood stem cell transplantation. J Hematother Stem Cell Res. 2000;9:727-736.
26. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte specific antigen. J Immunol. 1980;125:1678-1685.
27. Horwitz SM, Breslin S, Negrin RS, et al. Adjuvant rituximab after autologous peripheral blood stem cell transplant results in delayed immune reconstitution with increase in infectious complications [abstract]. Blood. 2000;96:707a.
28. Flohr T, Hess GR, Kreiter S, Meyer RG, Huber C, Derigs G. Immune reconstitution after autologous CD34-positive selected peripheral blood stem cell transplantation combined with rituximab for refractory B-cell non-Hodgkin's lymphoma [abstract]. Blood. 2000;96:709a.