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Rituximab, Dexamethasone, Cytarabine, and Cisplatin as Effective Platinum-Based Salvage Chemotherapy for Periportal Posttransplant Lymphoproliferative Disorder After an Orthotopic Liver Transplant

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Abstract

Posttransplant lymphoproliferative disorder is a group of heterogeneous disorders that occur after solid-organ transplant. The overall incidence is between 1% and 20%. In orthotopic liver transplant recipients, the reported incidence ranges from 2% to 10%, while the incidence is greater in children (9.7%–11%) and lesser in adults (1.7%–3%). The following treatment options are considered for patients with posttransplant lymphoproliferative disorder: reduction of immunosuppression, single-agent rituximab, rituximab and chemotherapy, surgery and radiation, antivirals targeted at the Epstein-Barr virus, and cytotoxic T-lymphocytes targeting the Epstein-Barr virus.

This report describes a 61-year-old man who presented after an orthotopic liver transplant with a large periportal soft tissue mass that was shown on biopsy to be a monomorphic, CD20+, diffuse, large B-cell lymphoma, nongerminal center type. He was treated with reduced immunosuppression, followed by single-agent rituximab, then with an anthracycline-based chemotherapy regimen: rituximab, etoposide, prednisone, vincristine, doxorubicin, and then a platinum-based salvage chemotherapy with rituximab, dexamethasone, cytarabine, and cisplatin with a good response.

Case Report

The patient is a 61-year-old man who presented with chronic liver failure and hepatocellular carcinoma; his disease was within the Milan criteria for orthotopic liver transplant. His

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medical history was significant for hepatitis C virus, esophagogastric varices, portal hypertension, sigmoid diverticulitis, cirrhosis, hepatocellular carcinoma after undergoing a laparoscopic microwave ablation, coronary artery disease with previous left anterior descending bare metal stent placement, and diabetes mellitus. The results of his laboratory studies demonstrated chronic hepatitis C, anemia of chronic disease, and diabetes.

The patient underwent an orthotopic liver transplant. Induction immunosuppression included basiliximab with a rapid prednisone taper. Maintenance immunosuppression included cyclosporine and mycophenolate mofetil. His postoperative course was significant for multiple readmissions for elevated liver function test results. Epstein-Barr virus polymerase chain reaction was positive with 25 026 copies/mL, and he was started on valganciclovir. An endoscopic retrograde cholangiopancreatography demonstrated an anastomotic biliary stricture, and 2 stents were placed. The results of a liver biopsy were indeterminate for acute rejection, with a rejection activity index score of 2/9. A Doppler ultrasound of the liver demonstrated abnormal soft tissue in the periportal area encasing the main portal vein. Computed tomography scans of the abdomen and pelvis were performed for metastatic disease versus posttransplant lymphoproliferative disorder (PTLD). Magnetic resonance imaging of the abdomen and nuclear positron emission tomography lymphoma scans also were performed. The positron emission tomography scan demonstrated a large metabolically active lesion in the periportal area (Figure 1). Endoscopic ultrasound-guided fine needle aspiration of the mass was suspicious for malignancy.

An open biopsy specimen of the soft tissue mass demonstrated monomorphic PTLD diffuse large B-cell lymphoma type, CD20+, with ki-67+ in > 90% of the tumor cells. The results of a bone marrow biopsy specimen were negative.

As first-line treatment for PTLD, the patient underwent reduction in immunosuppression followed by single-dose rituximab. A liver magnetic resonance imaging scan demonstrated an enlargement of the mass. The patient then completed one cycle of anthracycline-based chemotherapy regimen: rituximab, etoposide, prednisone, vincristine, doxorubicin, and an additional 5 cycles of anthracycline-based chemotherapy regimen: rituximab, etoposide, prednisone, vincristine, doxorubicin with 25% vincristine (the dosage was reduced for neuropathy) (Figure 2). The patient had elevated liver function test results after the sixth cycle. A positron emission tomography scan was performed that was consistent with primary refractory disease, and platinum-based salvage chemotherapy with rituximab, dexamethasone, cytarabine, and cisplatin was started for monomorphic Epstein-Barr virus and associated PTLD that were refractory to therapy. The most recent positron emission tomography scan in January 2014 demonstrated a significant response to treatment (Figure 3).

Discussion

Posttransplant lymphoproliferative disorders are a heterogeneous group of complications that occur after bone-marrow or solid-organ transplant. The overall incidence of PTLD ranges from 1% to 0%.^{1,2} In orthotopic liver transplant recipients, the reported incidence ranges from 1.7% to 11.1% with incidence being greater in children (9.7%–11%) and lesser in

adults (1%–3%).^{3–6} Approximately 60% to 85% of cases of PTLT are associated with Epstein-Barr virus infection.^{5,6} Estimates of 1-year survival after PTLT in all graft types range from 56% to 73%, with 5-year estimates falling between 40% to 61%.¹ The reported 1-, 5- and 10-year survival rates for posttransplant PTLT in liver recipients are 53.8% to 85%, 46.2% to 69%, and 55%.^{5,6}

Factors associated with increased risk of PTLT include Epstein-Barr virus infection, with Epstein-Barr virus-seronegative recipients receiving grafts from Epstein-Barr virus-seropositive donors at particular risk.^{2,5} Other risk factors for PTLT include type of transplant (lung, small intestine, and multivisceral greater than heart, lung, and liver greater than renal), age (greater for younger than 10 y and older than 60 y), intensity of immuno-suppression, length of aggressive treatment,^{2,4,5,7} and antilymphocyte antibodies.^{4,5} Acute rejection has not been shown to be a risk factor for PTLT.⁷ Whether or not hepatitis C virus infection is a risk factor for PTLT is controversial.

Risk factors for mortality in orthotopic liver transplant patients with PTLT include elevated levels of lactate dehydrogenase, stage III or IV PTLT (Ann Arbor Staging System for Lymphoma), and hepatitis C virus infection.⁶ Other studies have reported no increased risk of mortality with hepatitis C virus infection.⁸ Additional factors reported to decrease survival include increased age at diagnosis, organ dysfunction, and multiple organ involvement with PTLT.¹¹ Patients who undergo a transplant for alcoholic cirrhosis have a similar risk for PTLT as other patients, but much greater long-term mortality (87% vs 50%).⁵ The presence of Epstein-Barr virus does not affect mortality.⁵ The following factors are associated with better survival: being a child, patients undergoing a transplant during tacrolimus immunosuppression, having polymorphic PTLT, and having limited disease.⁵

In orthotopic liver transplant patients who develop PTLT, the 3 most common sites of involvement are the lymph nodes, the gastrointestinal tract, and the liver.⁵ Patients presenting with PTLT of the graft liver frequently have inappropriate results of their liver function tests.⁴

Patients present with symptoms that are variable and nonspecific. These may include mild fever, mononucleosislike syndrome, lymphadenopathy, recurrent infections of an unknown origin (which may be resistant to antibiotics), and severe organ dysfunction. Final diagnosis is always based on histopathology.^{2–7} Computed tomography, magnetic resonance imaging, and positron emission tomography/computed tomography have been used to locate lesions and to help evaluate treatment success.

The World Health Organization classification of PTLT establishes the following categories: (1) Early lesions including plasmacytic hyperplasia and infectious-mononucleosislike PTLT, (2) polymorphic PTLT, (3) monomorphic PTLT (B- and T/NK-cell types), and (4) classic Hodgkin lymphoma type PTLT.^{9,10} More than 85% of PTLTs derive from B cells, 14% from T cells, and about 1% from natural killer cells.^{2,10} The most common form of monomorphic PTLT is diffuse large B-cell lymphoma.²

No standard algorithm exists for treating PTLT.⁸ Treatment often begins with reduction in immunosuppression with response typically observed in 2 to 4 weeks.^{2,7,9} In a retrospective

study of 42 patients, Tsai and associates¹¹ reported that 63% of patients responded to reduction of immunosuppression (mean time to response, 3.6 wk). The following factors were independent prognostic factors for lack of response: increased age, elevated lactate dehydrogenase, organ dysfunction, and multiorgan involvement.¹¹

In patients who fail initial reduction in immunosuppression or who are unlikely to respond, rituximab, a chimeric mouse/human monoclonal antibody against CD20, which leads to depletion of mature B lymphocytes, should be considered.⁷ In a phase 2 trial by Blaes and associates¹² investigating the use of single-agent rituximab in 11 patients with diffuse large B-cell lymphoma or a polymorphous process, the overall response rate was 64%, and the median survival rate was 14 months.

The use of a chemotherapy regimen including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) provides a response rate of 65%, median progression-free survival of 13.9 months, and overall survival of 42 months.¹³ Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) are the standard of care for nontransplant B-cell lymphomas and have been shown to be effective in achieving long-term disease-free survival.⁷ In a retrospective analysis of patients receiving anthracycline-based chemotherapy regimens as first-line therapy combined with reduced immunosuppression, patients showed a complete response rate of 69% and a 5-year disease-free survival of 62% with little toxicity.⁷ Several authors have studied combined reduction of immunosuppression, rituximab, and chemotherapy. Podoltsev and associates¹⁴ specifically looked at patients with monomorphic PTLT and determined that a combination of complete withdrawal of immuno-suppression and R-CHOP led to a 90% response rate.

Acyclovir, ganciclovir, and valacyclovir are nucleoside analogues that inhibit Epstein-Barr virus DNA replication, by inhibiting viral DNA polymerase.⁷ The agent of choice is ganciclovir. Antivirals are of unproven benefit because cells containing latent Epstein-Barr virus or cells of Epstein-Barr virus-associated lymphomas do not express thymidine kinase, an enzyme necessary for their activation.^{2,7} When antiviral treatment is preceded by administering arginine butyrate (an inducer of the Epstein-Barr virus lytic cycle), an overall response of 83% was reached in patients with refractory Epstein-Barr virus-positive lymphoid malignancies.¹⁵

Radiotherapy and surgery also are options for treatment. These are more likely to be recommended when PTLT is limited to a single localized lesion.²

Potential future targets for therapy include interleukin-6 and galectin-1. Galectin-1 is expressed heavily by Epstein-Barr virus-transformed lympho-blastoid B-cell lines and primary PTLTs exhibit strong expression of galectin-1. Interleukin-6 promotes proliferation of Epstein-Barr virus-infected B cells.⁷ An Epstein-Barr virus vaccine also is being developed, but this is controversial.

In conclusion, although the standard treatment for PTLT is primarily reduction in immunosuppression, for some patients additional treatment options must be sought. In our 61-year-old man with periportal PTLT after orthotopic liver transplant who failed standard therapy with reduction in immunosuppression, single-agent rituximab and anthracycline-

based chemotherapy regimen: rituximab, etoposide, prednisone, vincristine, doxo-rubicin, platinum-based salvage chemotherapy with rituximab, dexamethasone, cytarabine and cisplatin served as an effective salvage chemotherapeutic regimen.

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Figure 1.
Positron Emission Tomography/Computed Tomography: Pretreatment

Figure 2.
Positron Emission Tomography/Computed Tomography: After 5 Cycles of Anthracycline-Based Chemotherapy Regimen With Rituximab, Etoposide, Prednisone, Vincristine, and Doxorubicin

Figure 3.
Positron Emission Tomography/Computed Tomography: After 1 Cycle of Platinum-Based Salvage Chemotherapy With Rituximab, Dexamethasone, Cytarabine, and Cisplatin