To the editor:

Severe human herpesvirus-8 primary infection in a renal transplant patient successfully treated with anti-CD20 monoclonal antibody

Infection with HHV-8 in transplant recipients has been associated with severe HHV-8 primary infection and is responsible for the death of 3 of the 5 reported cases.1-4 Here we report a case of severe HHV-8 primary infection that was transmitted through a renal allograft and successfully treated with rituximab.

A 47-year-old man, seronegative for HHV-8, received a first renal transplant from an HHV-8 seropositive cadaveric donor to treat end-stage renal failure due to nephroangiosclerosis. Eight months later, the patient was hospitalized due to fever, night sweats, pharyngeal pain, and weakness. Upon physical examination, weight loss, hepatosplenomegaly, and pharyngeal erythema were found, and laboratory tests showed pancytopenia. Bone marrow aspiration showed normal cellularity, with a slight excess of myeloblasts, dysplastic maturing granulocyte precursors, moderately plasmacytosis, and no evidence of hemophagocytosis. Routine blood and urines cultures for common bacterial and fungal pathogens were negative. No evidence of type 1 or type 2 herpessviruses, varicella-zoster virus, Epstein-Barr virus, or parvovirus B19 DNA was detected in the patient’s serum. Severe HHV-8 primary infection transmitted through the renal allograft was suspected and was confirmed by the detection of HHV-8 DNA by quantitative polymerase chain reaction (PCR) assay in peripheral blood mononuclear cells (PBMCs), bone marrow, and pharyngeal samples.

Despite a drastic reduction of the immunosuppression (Figure 1), the patient’s clinical condition worsened, and rituximab was started with the written informed consent of the patient. Its initiation was followed by a rapid reduction of circulating B cells and was associated with a dramatic improvement in the patient’s general condition (Figure 1A) and performance status. Hepatosplenomegaly and pharyngitis were no longer found on physical examination 2 weeks after the beginning of treatment. At one month, both routine laboratory tests and bone marrow aspiration were normal. The HHV-8 load in PBMCs started to fall after the first infusion of rituximab and became negative after the third infusion (Figure 1C), as did the levels of serum interleukin 6 (IL-6) and IL-10 (Figure 1B). The patient was finally discharged the day after the fourth injection of rituximab.

After a follow-up of 3 years, the patient is clinically well, and neither Kaposi sarcoma nor lymphoproliferative disease has been diagnosed. Serologic tests remain negative for HHV-8 LANA-1, and HHV-8 DNA in PBMCs remains undetectable by PCR assay.

We resorted to rituximab as rescue therapy because we postulated that the rapid eradication of HHV-8–infected B cells5 might reduce viral burden and prevent the proliferation and activation of reactive T cells and macrophages. Our decision was further supported by previous demonstrations that CD20 antigen was expressed by HHV-8–infected cells6,7 and later by the results reported by Milone et al8 for 2 patients with primary Epstein-Barr virus infection and X-linked lymphoproliferative disease.

Although further studies are required to confirm this efficacy, we believe that rituximab therapy should be considered as the initial management of severe HHV-8 primary infection.

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References


To the editor:

Mutagenic potential of temozolomide in bone marrow cells in vivo

Therapy-related myeloid leukemias (t-MLs) occur in as many as 5% to 10% of patients who are otherwise cured of a primary neoplasm with aggressive multimodal regimens. Many patients with t-MLs or therapy-related myelodysplastic syndrome (t-MDS) have previously received chemotherapeutic agents that alkylate DNA, such as bis-chloroethyl-nitrosourea (BCNU) and cyclophosphamide (CP). We and other investigators have shown CP to be mutagenic in preclinical studies both in vitro and in vivo. Temozolomide (TMZ) is a more recently developed alkylating agent that has been effective in the treatment of adult high-grade glioma and refractory leukemia. TMZ is now being incorporated into initial therapy in more than 40 studies for a range of cancers, including glioblastoma and melanoma. TMZ’s cytotoxicity depends on the methylation of guanine bases at the O6 position, resulting in O6-methylguanine and G:C→A:T transitions. Despite initial hopes that TMZ would be less leukemogenic than traditional alkylating agents, 2 groups have recently reported secondary myeloid malignancies after TMZ treatment in clinical studies. As TMZ moves into the front line of our chemotherapeutic armamentarium, further investigation of its in vivo mutagenic potential is warranted.

We used a transgenic mutation indicator mouse strain (small blue mouse) to compare the in vivo mutagenic potential of TMZ on bone marrow (BM) cells with that of CP. In this mouse model, the mutational target is the nontranscriptionally active lacZ portion of the plasmid pUR288. The mutation frequency was determined with a plasmid rescue procedure applied to genomic DNA derived from BM and with a subsequent selection for lac-Z negative clones, according to published protocols. The type of mutation was further determined by PCR amplification and restriction digestion.

Animals were treated with TMZ (175 mg/kg/d intraperitoneally for 5 days), CP (200 mg/kg intraperitoneally either once or weekly for 6 weeks), or phosphate-buffered saline (PBS), and BM was harvested 10 days after the last treatment (Figure 1). TMZ and CP doses were chosen by treating C57BL/6 mice in groups of 10 to 20 until the development of neutropenia without mortality. Determination of the mutation frequency revealed that the 1-day CP treatment increased the mutational load in BM 2-fold over the control, whereas the TMZ regimen resulted in a 22-fold increase over control. BM cells in animals treated 6 times with CP did not show an increase in the mutation frequency over animals treated with only a single dose of CP. As we expected from TMZ’s mechanism of action, over 90% of all mutations in response to TMZ treatment were point mutations. Fewer than 30% of the mutations in BM cells from animals treated with CP were point mutations, with the remaining mutations being either translocations or deletions. These data emphasize TMZ’s mutagenic potential for BM cells in vivo in the mouse model system and may indicate that TMZ’s mutagenic potential is the underlying cause of the recently reported t-MLs in TMZ-treated patients. We suggest close long-term hematological monitoring of patients receiving TMZ in clinical trials. Further investigation is warranted to determine whether the increased mutation rate seen with TMZ exposure results in a comparable elevated risk of therapy-induced leukemia.

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References

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