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Guillain-Barre' syndrome following varicella zoster reactivation in chronic lymphocytic leukemia treated with fludarabine

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Varicella zoster virus (VZV) infection followed by Guillain-Barre' syndrome occurring in chronic lymphocytic leukemia (CLL) after fludarabine treatment has not previously been described. We report the case of a patient who completed fludarabine treatment and after 2 months developed Guillain-Barre' syndrome preceded by a recent history of cutaneous herpes zoster. With the increasing use of fludarabine, expecially in CLL, consciousness of such complications is important because of their potentially serious consequences. A 60-year-old woman with chronic lymphocytic leukemia stage B/III was treated with fludarabine 25 mg/m^2 for 5 d for four courses, from December 2000 to March 2001 as first-line treatment. At the start of the treatment she showed WBC 43,940/µL (N 2,850/µL, L 33,120/µL), Hb 10.9 g/dL, Plts 193,000/µlL normal values of immunoglobulins except for IgG 722 mg/dL (range 800- 1800) and positivity for antibody IgG against herpes simplex, varicella and cytomegalovirus. She received prophylaxis with oral trimethoprim/sulphametoxazole twice a week. During the last two cycles the dosage of fludarabine was reduced to 15 mg/m^2 because of mild leukopenia (WBC 2000/µL, N 1100/µL, L 740/µL as minimum value). In May 2001 she obtained partial remission with persistent mild leuko-lymphocytopenia (WBC 2,140 µl, N 1,420 µl, L 530/µL), normalization of immunoglobulin levels (IgG 1024 mg/dL, IgA 190 mg/dL, IgM 52 mg/dL), marked B lymphopenia: CD19+ 11/µL (normal value: 160-290) and T lymphopenia: CD3+ 376µL (range 1,185-1,540), CD4+ 180/µL (range 670-950) and CD8+ 180/µL (range 505-695); normal values of effector cells (CD16/56+ 138/µL) Fifteen days after re-evaluation she developed the typical healing skin lesion of zoster, accompanied by pain and dysesthesia of the right gluteus and perineum affecting S2-S4 right dermatomes. She started treatment with acyclovir 800 mg five times a day. Two weeks later, she first developed a peripheral bilateral palsy of the facial nerve, and then weakness of legs with ataxic gait. Neurologic examination showed a severe, bilateral facial weakness, decreased power in both proximal and distal limb muscles (MRC=3), bilaterally, with absence of tendon reflexes. She could walk only with assistance due to ataxia. CSF analysis showed an increase of protein content 75 mg/dL (range 20-40); PCR on CSF was negative for detection of viral genome of CMV, HSV, VZV and Rubeovirus. Electrophysiological examination showed an increase of distal latencies, prolonged F wave latencies and a marked reduction of the amplitude of sensory action potentials; motor and sensory conduction velocities were within normal limits, no conduction blocks were observed. A diagnosis of Guillain-Barre' syndrome was made and treatment with intravenous human immune globulins (0.4 mg/Kg/d for 5d) was started. The patient improved slowly and 6 months later she was completely asymptomatic in continuous complete remission of her CLL. Traditionally, patients with CLL were treated with chlorambucil with or without corticosteroids, but also other alkylating agent-based regimens have been used.[1] Fludarabine in CLL induces a very high response rate, with a substantial number of complete remissions in previously treated patients with CLL.[2] Compared to chlorambucil and CHOP, fludarabine produces a higher clinical remission rate and delayed time of retreatment, but no differences in overall survival have been demonstrated.[3] After fludarabine treatment, the CD4+ and CD8+ T-lymphocyte

subpopulations decrease to levels of 150-200/μL and the recovery towards normal levels is slow.[2] Bacteremia, *Pneumocystis carinii* pneumonia, Aspergillus pneumonia, disseminated CMV, systemic candidiasis, localized herpes zoster (up to 50%) Ref 4 and reactivation of herpes simplex are the more commonly observed infective complications of fludarabine therapy for hematologic malignancies.[5,6] Infections seem to occur more often in previously treated than in previously untreated patients[7] suggesting that the severity of immunosuppression might be potentiated by extensive prior treatment.[8] Keating reported that the incidence of infections occurred while patients were in remission off-treatment and the most common single event was dermatomal herpes zoster. We noticed a similar setting after selected CD34+ peripheral blood progenitor cell transplantation for lymphoproliferative disease, in which the high rate of viral complications is probably due to the inability of residual T cells left from the CD34+ cell selection to generate an adequate number of virus-specific lymphocytes.[9] At the time of the presentation of VZV infection and Guillain-Barre' syndrome the patient showed a reduction of humoral and cellular immunity, with low levels of total T and B lymphocytes including T-helper, T-suppressor subsets resulting in an defective cooperation against infections. With the increased use of fludarabine for treatment of CLL we agree with other authors who underline the importance of educating patients and the need to define the role of viral prophylaxis to avoid unpredictable complications.[4,6]

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