Chronic myeloid leukemia associated with mitoxantrone treatment in a patient with MS

Saud A. Sadiq, Mustapha Rammal and Gabriel Sara

We report the first case of chronic myeloid leukemia (CML) in a patient with multiple sclerosis (MS) diagnosed within two years of receiving mitoxantrone therapy. Previously only acute forms of leukemia particularly acute promyelocytic leukemia (APL) have been associated with mitoxantrone treatment in MS. This underscores the need for only using mitoxantrone in severe treatment-unresponsive cases of MS. Multiple Sclerosis 2008; 14: 272–273. http://msj.sagepub.com

Key words: chronic myeloid leukemia; multiple sclerosis; mitoxantrone

Introduction

Mitoxantrone is an FDA approved medication for the treatment of severe relapsing and remitting MS and for worsening progressive MS. It is associated with acute myelogenous leukemia (AML) probably because it interferes with DNA repair mechanisms by inhibiting topoisomerase II [1,2]. In MS, the incidence of mitoxantrone-associated AML is unknown as every patient on such therapy has not been closely followed, but is estimated to be in the range of 0.5–2% [3,4]. In a study of 802 patients, two patients developed AML and additional patients have been reported in the Registry to Evaluate Novantrone Effects in Worsening MS (RENEW study) [4–6]. We report the first case of chronic myeloid leukemia (CML) in a patient with MS diagnosed within two years of receiving mitoxantrone therapy.

Case report

In 1995, a previously healthy 38-year-old woman experienced right hand numbness, which progressed to involve both hands and limbs over the next 24 h. There was no prior history of any episodes of transient neurological dysfunction, or any significant infectious diseases such as Lyme’s disease. The rest of her history was non-contributory and in particular she had no history suggestive of connective tissue disorders. There was no family history of cancer. Examination revealed minimal weakness in her left deltoid and bilaterally in her hand grip. She had bilateral iliopsoas weakness (4+ on MRC scale) and positive Lhermitte and Rhomberg signs with decreased vibratory sense in her lower limbs. The rest of the neurological examination was unremarkable. Brain magnetic resonance imaging (MRI) revealed multiple periventricular white matter lesions with the largest lesion at the junction of the body and genu of the corpus callosum on the left. Cervical spine MRI revealed some patchiness at the C1–C2 junctions but was otherwise unremarkable. Routine blood tests including CBC, liver and renal function tests were normal. Screening tests for rheumatological and infectious diseases were negative and spinal fluid analysis revealed normal protein, glucose, one WBC and no oligoclonal bands were detected. She was treated with IV methylprednisolone with good recovery over several weeks. In January 1996, she complained of profound fatigue for several weeks and in April 1996, had new onset of neck pain and tingling associated with an unsteady gait. At the time C-spine MRI revealed enlargement and better definition of the previously noted lesion. She was commenced on β-interferon 1A therapy for clinically definite MS. In 1998, she unexpectedly became pregnant and had to discontinue β-interferon 1A. Two months after delivery,
she was restarted on β-interferon. In March 2000, she had a clinical relapse manifested by sensory symptoms and bladder/bowel dysfunction. In January 2001, she had optic neuritis of her left eye, which was treated with three days of IV methylprednisolone. She had two further relapses in early 2001 with increasing disability of gait. At the time, brain MRI showed increased T2 lesions compared with a 1999 scan. C-spine MRI revealed a 2.5 cm C1–C3 lesion in the central aspect of the spinal cord. Because of her worsening clinical status, she was started on mitoxantrone treatment in September 2001, and received 18 mg (12 mg/m²) every two months until 2 February 2003 (total of eight doses). Her weekly β-interferon 1A treatment was continued during this period. Her disease stabilized and no further relapses occurred. During the course of her mitoxantrone treatment, her blood counts remained normal except in the post-treatment nider, when here total white cell counts ranged from 2000–3000/cm³. From February 2003 to July 2004, she remained stable on β-interferon 1A monotherapy. In August 2004, a routine CBC revealed a leukocytosis of 14 700, which was thought to be associated with a urinary tract infection, which was treated. A repeat CBC in October 2004 showed a WBC of 31 400 and an absolute neutrophil count of 24 806 with elevations of metamyelocytes, myelocytes and basophils. In addition, there was thrombocytosis with a platelet count of 663 000 and an elevated alkaline phosphatase of 131 u/L. A bone marrow examination revealed hypercellular marrow with granulocytic predominance with cytogenetic positivity for chromosome 9 and 22 and FISH positive for bcr-abl in 100% of nuclei. The patient was diagnosed with chronic myelogenous leukemia and started on Gleevec 400 mg on November 2004. After initial complete clinical and bone marrow remission, she developed a blast crisis in July 2006 and transformed to acute myeloid leukemia. She is currently status post allogeneic peripheral blood stem cell transplant from a matched sibling donor.

Discussion

This is the first report of a patient developing CML in association with mitoxantrone therapy and the timing of onset of CML without a family history of leukemia makes it likely that this is a treatment-related complication. Mitoxantrone therapy is reserved for severe forms of multiple sclerosis because of a concern with infections, cardiac toxicity, menstrual dysfunction and secondary ovarian failure [7–9]. However, the most serious treatment complication is the occurrence of AML, usually of the promyelocytic subtype [2]. The frequency of mitoxantrone treatment-related acute leukemia is estimated to be less than 2% of all treated patients. However, as not all cases of AML are reported in the literature, the exact risk of developing leukemia may be underestimated. However, in our review of the literature, no cases of AML are reported in patients receiving less than five treatments of mitoxantrone, suggesting that this treatment maybe safe to use as a short term rescue treatment [6–8].

The occurrence of CML in our patient is enigmatic because CML is not a recognized complication of mitoxantrone therapy, even in cancer chemotherapy where higher drug dosages and combination therapy are routinely used. Whether this case represents a real but an extremely rare risk of mitoxantrone treatment or is a chance occurrence will be determined by continued close monitoring of all patients receiving mitoxantrone treatment.

References