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To the editor:

Dasatinib induces complete remission in a patient with primary cerebral involvement of B-cell chronic lymphocytic leukemia failing chemotherapy

Primary symptomatic central nervous system (CNS) involvement as the initial manifestation of chronic lymphocytic leukemia (CLL) is exceedingly rare.[1] Treatment options in patients resistant to high-dose cytarabine or methotrexate chemotherapy are limited. Dasatinib is a tyrosine kinase inhibitor of Bcr-Abl and Scr families that has shown activity in a limited number of cases with CLL in previous literature.[2,3] Because of its ability to cross the blood-brain barrier,[4] dasatinib could be useful in CLL cases with CNS involvement.

We report the case of a 68-year-old male with primary CNS B-cell CLL who experienced a relapse after 2 lines of chemotherapy and achieved an ongoing, long-lasting complete remission on dasatinib monotherapy as demonstrated by magnetic resonance imaging (MRI; Figure 1). He presented with paraparesis of both legs, urinary and stool incontinence, and central right-sided facial nerve palsy in our clinic after extensive diagnostic workup in a neurology department ruling out other causes like multiple sclerosis. MRI revealed cerebral lesions of the brain stem, the spinal cord, and the meninges. The cerebral spinal fluid (CSF) contained 146 cells/μL, exclusively lymphocytes, with no red-cell contamination. IgG was slightly elevated in the CSF, but there were no oligoclonal bands. CLL was confirmed by flow cytometry of the CSF identifying a monoclonal κ-positive lymphocyte population (16% of all lymphocytes) expressing $CD19^+$, $CD5^+$, $CD23^+$, $CD43^+$, $CD20^{low}$, $CD38^+$, $CD79b^-$, and $CD22^{low}$. All other cells were heterogeneous T lymphocytes. Complete differential blood count, serum immunoglobulins, lactic dehydrogenase, and β2-microglobulin were normal. Clinical examination revealed no hepatosplenomegaly or lymphadenopathy. Flow cytometric analysis of the bone marrow and peripheral blood showed a monoclonal B-cell population of 3% and 1%, respectively, with the above-mentioned phenotype.

Initial treatment included 5 courses of intravenous methotrexate (4 g/m^2/day over days 1-2) and ifosfamide (1.5 g/m^2/day over days 3-5), which led to rapid improvement of neurologic symptoms. At relapse, salvage chemotherapy included intravenous cytarabine (3 g/m^2 twice per day over days 1-2), mitoxantrone (10 mg/m^2/day

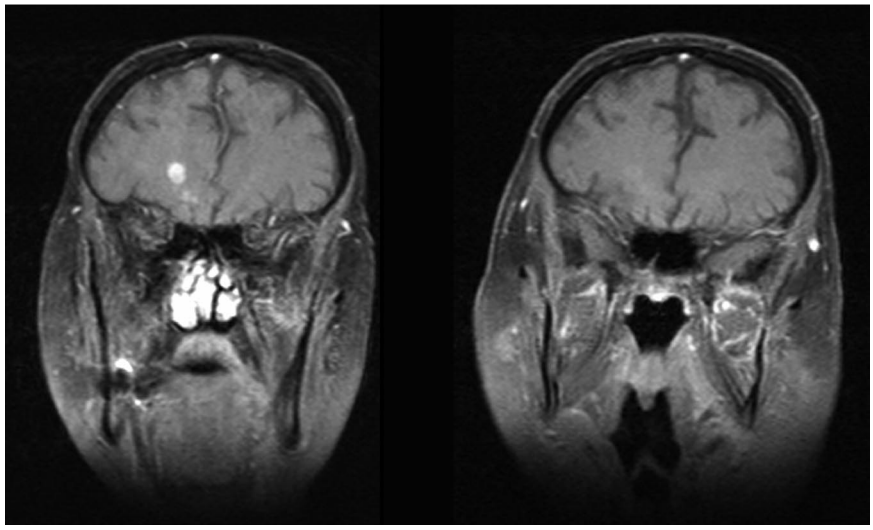

Figure 1. MRI scans before and during continuous dasatinib therapy. The left picture shows a representative MRI slice before dasatinib treatment. The right slide shows the same area approximately 9 months later. Pictures are representative of a total of 4 lesions with similar development.

over days 2-3), and intrathecal methotrexate (15 mg/day on day 1). Although initially successful, the patient later relapsed with an increase in the size and number of the cerebral lesions. Oral dasatinib (70 mg twice per day) was started and led to a complete regression of lesions visible on MRI and neurologic disease. The patient is currently in remission (> 12 months) with no measurable monoclonal lymphocyte population in blood and bone marrow on continuous therapy.

Pitini et al[2] and others[3] initially reported responses to dasatinib in patients with CLL, although subsequent phase 2 clinical trials in relapsed CLL demonstrated only moderate activity.[5] This is the first report of dasatinib treatment in central nervous system B-CLL and might serve as a proof of concept for future cases. In vitro data suggest that del(17p) mutated CLL and those with unmutated immunoglobulin heavy chains (IgVHs) might be especially sensitive to dasatinib.[2,5,6] Unfortunately, IgVH mutational analysis was not initially performed. Dasatinib CSF concentration is reported to reach only 5% to 28% of plasma concentrations in humans.[4] Still, the effect in this case was clinically meaningful and lasting. Further clinical investigation of dasatinib treatment in B-CLL with CNS involvement is warranted.

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To the editor:

Gemtuzumab ozogamicin: is there room for salvage?

On May 17, 2000, gemtuzumab ozogamicin received marketing approval from the US Food and Drug Administration (FDA) under accelerated approval regulations for the treatment of patients with CD33-positive acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.[1] The data supporting this application included 3 open-label studies that enrolled 157 patients at least 60 years of age in whom an overall response rate of 24% (12% CR + 12% CRp) was observed. On June 21, 2010, the FDA and Pfizer announced that this drug would be voluntarily withdrawn from the market due to failure of 2 confirmatory clinical trials to demonstrate clinical benefit. Of note, the confirmatory trials examined gemtuzumab as an addition to standard induction chemotherapy in newly diagnosed patients up to 70 years of age, rather than in a relapsed or refractory older population.

To those familiar with other attempts at improving outcomes in patients with newly diagnosed AML and with the hepatic toxicity of the approved dosing regimen of gemtuzumab, the failure of gemtuzumab to provide survival benefit when combined with anthracycline and cytarabine was not surprising.[2-4] It is, therefore, appropriate for the drug to be withdrawn from the market at this time given the accelerated regulatory pathway agreed upon previously. However, questions remain. Is there a role for this agent in a certain population of patients? Is there a safer method for administering the drug?

Data from uncontrolled studies clearly indicate that the drug has single-agent activity in the setting of relapsed or refractory AML in addition to having activity in acute promyelocytic leukemia.[1,5] In addition, a study of 57 patients with relapsed or refractory AML examined fractionation of the dosing of gemtuzumab by administering 3 mg/m^2 on days 1, 4, and 7 rather than the FDA-approved 9 mg/m^2 on days 1 and 8. Administration in this manner was not associated with any grade 3 or 4 hepatotoxicity.[6] The CR rate of 26% also indicated that efficacy appeared to be maintained when the drug was administered in this manner. In our own small series of 12 relapsed/refractory patients combining gemtuzumab with decitabine, we similarly observed absence of grade 3 or 4 hepatotoxicity with a response rate of 41%.[7]

There is a paucity of active agents effective for relapsed or refractory AML, particularly in older individuals. It was our hope