

Effectiveness of Dasatinib in Relapsed CNS, Ph+ ALL That is Refractory to Radiochemotherapy Plus Imatinib: A Case Report

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Introduction

The Philadelphia chromosome (Ph+) is present in more than 20% of patients with acute lymphoblastic leukemia (ALL).¹ Imatinib (Gleevec, Novartis) is a first-generation BCR-ABL tyrosine kinase inhibitor (TKI) that is part of frontline therapy for Ph+ leukemias. Remission rates of up to 90% can be achieved with the use of imatinib, whether administered alone or in combination with chemotherapy.²

Central nervous system (CNS) involvement is a common complication in Ph+ ALL,³ developing in 20% of patients who receive long-term imatinib therapy.^{3,4} In many cases, CNS involvement occurs despite complete remission in peripheral blood and bone marrow.⁴⁻⁶ This can be attributed to poor penetration of imatinib into the cerebrospinal fluid (CSF), with inadequate concentration for kinase inhibition.⁷ This may be in part due to the fact that imatinib is a substrate for the drug-eluting P-glycoprotein, which results in subtherapeutic levels of imatinib in the CNS.^{3,8}

Conventional therapy for CNS leukemia—including intrathecal chemotherapy, high-dose systemic chemotherapy, and radiotherapy—is unsatisfactory in many cases because most patients experience poor quality of life, significant systemic or CNS toxicity, short-lived responses, and ultimately death, resulting from refractory leukemia.⁹

Dasatinib (Sprycel, Bristol-Myers Squibb), a potent second-generation inhibitor of tyrosine kinases SRC and BCR-ABL, has shown significant activity in

adults with imatinib-resistant or imatinib-intolerant Ph+ ALL, with an in vitro potency 325-fold greater than imatinib for inhibiting BCR-ABL.^{8,10-15} Dasatinib has a chemical structure that is unrelated to imatinib, although both agents have overlapping binding sites within the ABL kinase domain.¹⁶ It is predicted that dasatinib, unlike imatinib, will bind to both the active and inactive conformations of ABL.^{1,16,17}

We report the case of a man with Ph+ ALL and CNS relapse, who responded well to dasatinib therapy after imatinib, high-dose chemotherapy, cranial radiation, and intrathecal rituximab failure.

Case Presentation

The patient is a 21-year-old man who has pre-B-cell Ph+ ALL with more than 50% bone marrow blast cells, and a negative CSF examination. Karyotype found that 20% of metaphases showed t(3;9;22)(q21;q34.1;q11.2), and molecular studies detected the p210 (b2a2) BCR-ABL fusion transcript. The patient began induction therapy with conventional chemotherapy combined with imatinib (400 mg/day), and bone marrow examination revealed less than 5% blast cells 14 days later. The patient achieved complete hematologic remission 1 month after chemotherapy and imatinib were started, but minimal residual disease in bone marrow was reported in 1.39% of ALL cells.

Three months after the diagnosis of leukemia, the patient underwent allogeneic peripheral blood stem cell transplantation using reduced intensity conditioning (Allo-RIC) from his identical human leukocyte antigen-matched brother. The non-myeloablative conditioning regimen consisted of intravenous (IV) cyclophosphamide 350 mg/m² daily for 3 days, IV fludarabine 30 mg/m²

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daily for 3 days, and oral busulfan 4 mg/kg daily for 2 days. Granulocyte colony-stimulating factor (10 µg/kg/day) was delivered to the donor on days -4 to +1. One apheresis procedure was performed on day 0 using a COBE-Spectra (Gambro, Lakewood, CO) machine. Enumeration of the total white blood cells, mononuclear (MNC) cells, and CD34-positive cells was done by flow cytometry in an EPICS Elite ESP apparatus (Coulter Electronics, Hiialeah, FL), using the anti-CD34 monoclonal antibody HPCA-2 (Becton Dickinson, San Jose, CA). The total number of CD34-positive cells obtained and infused in the patient was 7.39×10^6 /kg of the receptor's body weight. Graft-versus-host disease (GVHD) prophylaxis included oral cyclosporine and methotrexate. The patient had full engraftment with a platelet count of 50×10^9 /L on day +14, and 1.22×10^9 /L neutrophil count on day +18. Chimerism was evaluated by multilineage polymorphic markers (STRs). The patient had 87% donor chimerism on day +30; however, blast cells in CSF were reported on day +17.

One month after bone marrow transplant, the bone marrow was in partial remission with less than 5% blast cells, and the patient started conventional maintenance therapy, including daily purinethol and weekly methotrexate (4 cycles) plus imatinib. Intrathecal chemotherapy (cytarabine, methotrexate, and hydrocortisone) was administered on days -6, +3, +6, +13, +17, +24, +36, +48, and +56, but CSF tests were reported as positive for leukemic cells. Due to this failure, the patient underwent CNS radiotherapy at 180 cGy per session during 17 days (total 3,060 cGy); however, CSF remained positive for blast cells. The patient continued with imatinib and received 2 cycles of IV cytarabine 3 g daily for 2 days, plus weekly intrathecal rituximab for 5 weeks. Despite this, CSF tests remained positive for blasts. Donor chimerism was reported at 98%.

Thirty days after cytarabine and intrathecal rituximab failure, oral dasatinib was started at 50 mg twice daily and adjusted to 70 mg twice daily 2 weeks later. Imatinib and cyclosporine were discontinued, although intrathecal hydrocortisone (without rituximab, cytarabine, or methotrexate) was administered twice monthly every 3 months. CSF blasts disappeared 30 days after dasatinib was started, and the bone marrow showed no blasts (Figure 1). The patient continues on dasatinib and has completed 12 months with no blasts in the CSF analysis, and has normal bone marrow and peripheral blood counts.

Dasatinib was well tolerated by the patient, although it was temporarily discontinued for 1 week due to pancytopenia (hemoglobin, 7.3 g/dL; white blood cell count, 2.4×10^9 /L; neutrophils, 0.3×10^9 /L; and platelets, 84×10^9 /L) 5 months after its initiation. Remarkably, our patient has never presented with nonhematologic secondary effects of dasatinib, as commonly described in other papers.

Currently, the patient is asymptomatic with full chimerism, and in hematologic and molecular remission with no blasts in CSF; he is receiving only dasatinib.

Discussion

The introduction of imatinib in combination with chemotherapy has improved the prognosis of adults with Ph+ ALL; however, resistance to this drug is increasing.^{17,18} Also, despite peripheral blood and bone marrow responses, patients with Ph+ leukemia who receive prolonged imatinib therapy have developed isolated CNS disease due to poor drug penetration into the CSF, resulting in subtherapeutic levels of imatinib.^{7,19}

Dasatinib is a second-generation inhibitor of tyrosine kinases SRC and BCR-ABL that has been used in the treatment of imatinib-intolerant or -resistant Ph+ leukemias.^{1,15,16,20} This drug has been shown to be effective and well tolerated in adults with Ph+ ALL at a recommended dose of 70 mg twice daily.²⁰ In the START-L (SRC/ABL Tyrosine Kinase Inhibition Activity Research Trials of Dasatinib) phase II study, a complete hematologic response was achieved in 31% of the 36 adults receiving dasatinib for Ph+ ALL that was resistant or intolerant to imatinib.¹⁵ In this study, dasatinib therapy was associated with a median overall survival of 8 months, with 22% of the patients alive and progression-free 1 year after starting treatment.

An analysis of the crystal structure of dasatinib-bound ABL-kinase suggests that the higher affinity of dasatinib for the ATP-binding site of the BCR-ABL tyrosine kinase domain compared with imatinib is due to the ability of dasatinib to bind the kinase in multiple states, both the active and inactive forms.^{1,16,17}

Preclinical data show that dasatinib crosses the blood-brain barrier.⁷ On this basis, some investigators assume that dasatinib may represent an effective therapy for Ph+ CNS leukemia. Porkka and colleagues reported the effectiveness of dasatinib therapy in CNS relapse in a chronic myelogenous leukemia (CML) rat model. They also demonstrated that CSF dasatinib concentration, despite being 12–31-fold lower than in plasma, was enough to produce CNS antileukemic activity.⁸

The superior effectiveness of dasatinib over imatinib against Ph+ CNS leukemia could be due to the much greater potency (325-fold) of dasatinib over imatinib,^{8,10-15} allowing the achievement of a therapeutically effective concentration of dasatinib, which has been shown to be active at low concentrations.¹⁴ Such increased potency, along with the fact that the CSF is a low-protein environment where dasatinib is likely to exist as a free drug, suggest that even if dasatinib levels in the CNS are relatively low, dasatinib concentrations achieved are sufficient for antitumor activity.⁸

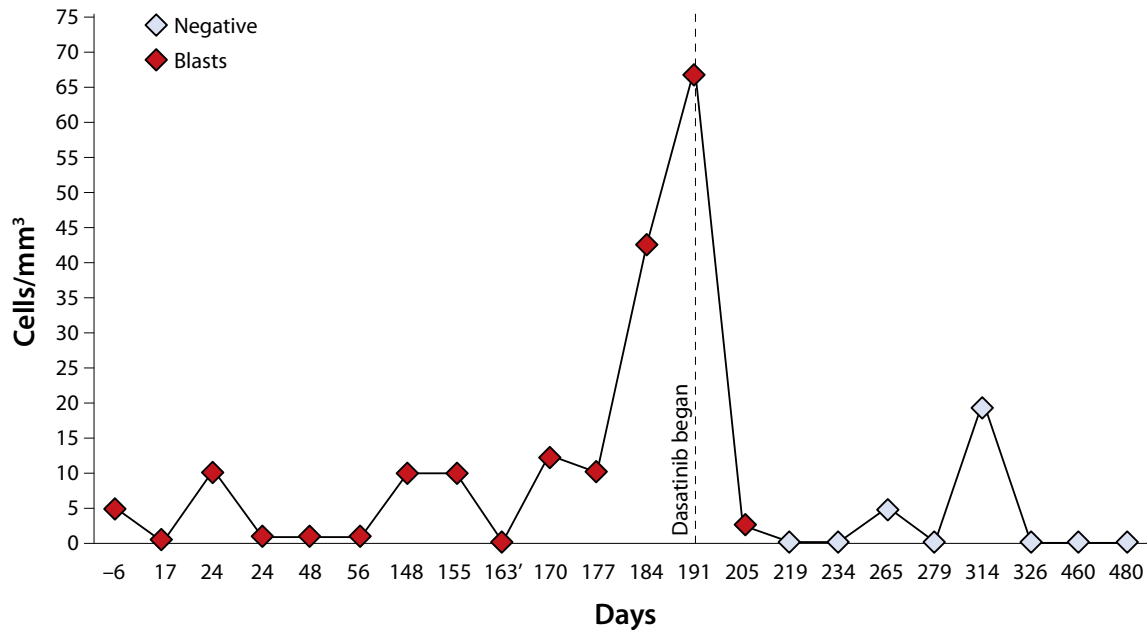


Figure 1. Reduction in cerebrospinal fluid cell counts induced by dasatinib. Cerebrospinal fluid on days 265 and 314 was contaminated with blood cells without blast cells.

Another possibility relates to the differential susceptibility of imatinib and dasatinib to drug efflux pumps, such as multidrug resistance protein 1 (P-glycoprotein), which is highly expressed in hematopoietic stem cells. Imatinib is a substrate of P-glycoprotein,^{3,8} whereas dasatinib is not. Dasatinib may therefore achieve a higher intracellular concentration than imatinib. A third possibility is that the many additional kinases that are targeted by dasatinib contribute to a cytogenetic response.¹⁷

We describe the case of a young man with Ph+ ALL with infiltration to the CNS. In spite of the good response to allogeneic peripheral stem cell transplant and achievement of full chimerism with normal peripheral blood counts and marrow remission, the patient had a refractory Ph+ ALL in the CNS that was resistant to imatinib, intrathecal chemotherapy, intrathecal rituximab, and cranial radiation. In our patient, the correlation between the beginning of dasatinib treatment and the complete response with negative CSF tests was evident. He presented a dramatic decrease of CSF blasts, and 3 months after beginning dasatinib therapy, his CSF was normal with no leukemia.

Most drug-related adverse reactions to dasatinib are mild to moderate, including fluid retention, diarrhea, skin rash, headache, hemorrhage, fatigue, nausea, and dyspnea.^{1,16} Our patient tolerated dasatinib well; however, pancytopenia developed 5 months after starting the drug. Some level of hematologic toxicity is expected during

dasatinib therapy. Fortunately, cytopenias are reversible and can be managed with dasatinib dose modifications or interruption,^{1,16,17,19} as was done in our patient.

The data suggest that dasatinib may represent a treatment option for Ph+ ALL patients with CNS involvement who are unable or unwilling to undergo multiple intrathecal chemotherapy doses and/or cranial radiation. Based on the summarized evidence, we believe that the use of dasatinib as first-line therapy for imatinib-resistant Ph+ CNS leukemias deserves further investigation. Dasatinib could also be included in the allo-RIC conditioning for Ph+ ALL patients, with or without CNS involvement. However, although dasatinib appears to be an effective therapy for Ph+ ALL CNS relapse with no severe long-term adverse effects, controlled clinical trials with a representative number of cases are needed to properly establish its usefulness and safety profile.

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Review

Which Tyrosine Kinase Inhibitor, if Any?

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Introduction

Gutiérrez-Aguirre and colleagues describe a patient with Philadelphia chromosome-positive (Ph⁺) acute lymphoblastic leukemia (ALL) who developed central nervous system (CNS) leukemia after being allografted employing a reduced intensity conditioning regimen.¹ The patient was successfully treated with dasatinib after failing treatment with imatinib. The case allows for some reflections regarding the treatment of patients with Ph⁺ ALL in the era of tyrosine kinase inhibitors (TKIs). Dasatinib is a

potent BCR-ABL inhibitor that is effective in chronic myeloid leukemia, as well as in Ph⁺ acute ALL that is resistant or intolerant to imatinib. Findings from a recent study conducted in Italy have shown that in adult Ph⁺ ALL patients, induction treatment with dasatinib plus steroids was associated with a complete hematologic response in virtually all patients, irrespective of age and compliance, and regardless of the fact that there were no deaths and a very rapid debulking of the neoplastic clone.² The post-remission therapy of patients with Ph⁺ ALL remains controversial, but allogeneic stem cell transplantation (SCT) is an adequate option in select cases.³

TKIs are expensive drugs, and are regrettably unaffordable for many patients living in developing countries.⁴ Imatinib was the first TKI introduced in México. Dasatinib and nilotinib are now available as well. Using the conventional doses of these 3 TKIs, their costs in México range from \$70–150 per day. In other countries, the price ranges are completely different. Curiously, some TKIs are more expensive in México than in developed countries. In 2012, imatinib will become available as a generic drug in México, and this will most likely result in a reduction of its price, thus making it available to a larger number of patients. In the case presented by Gutiérrez-Aguirre and colleagues, selecting the TKI that was to be used for treatment relied solely on the differential ability of the drug to penetrate the CNS. These types of factors should ideally be the only ones to consider when choosing a specific drug for patients. In developing countries, therapeutic decisions should ideally rely on both economic aspects

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and evidence-based medicine. Therapeutic trends, such as the use of new and oftentimes very expensive drugs, should be reserved for specific trials, and adopted into routine patient care practices only after carefully evaluating the cost-benefit ratio.

Regarding the cost of new drugs, it is interesting to mention that in March 2011, the National Institute for Health and Clinical Excellence (NICE) in England approved azacitidine for patients with myelodysplastic syndromes. The institute, which provides independent recommendations on treatments, published its final guidelines for the drug following an initial assessment, in which they ruled that it was not cost-effective. During the process of drafting the drug recommendations, the manufacturer of azacitidine offered to provide the drug at a reduced price, and this discount enabled its recommendation as a cost-effective use of resources.⁵ This decision will benefit many patients in the United Kingdom. In developing countries, we look forward to

these types of actions in the distribution of new and effective drugs, with the hope that they will become available to a greater number of patients.

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ERRATUM

Due to an editorial oversight, the order of the author names for the case study “Hematuria—A Rare Presentation of Hodgkin Lymphoma” was incorrect. The correct citation is as follows: Dembla V, Walker BN, Elkins SL, Files JC. Hematuria—a rare presentation of Hodgkin lymphoma. *Clin Adv Hematol Oncol*. 2011;9:788-790.