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CASE REPORT

# Dasatinib for a child with Philadelphia chromosome–positive acute lymphoblastic leukemia and persistently elevated minimal residual disease during imatinib therapy

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## ABSTRACT

Imatinib has improved outcomes in patients with Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL). Minimal residual disease (MRD) is a useful tool for predicting leukemia relapse. However, there is no consensus on how to treat children with elevation of *BCR-ABL* transcripts but no evidence of hematologic relapse during chemotherapy combined with imatinib. Here, we report the case of a child with Ph+ ALL who had persistent elevation of MRD, but no evidence of hematologic relapse while receiving imatinib plus intensive chemotherapy. Dasatinib was substituted for imatinib because no suitable donor for allogeneic hematopoietic stem-cell transplantation (HSCT) was available. Less-intensive chemotherapy with methotrexate and 6-mercaptopurine was administered concomitantly. No serious adverse events were encountered. With continuous dasatinib combined with chemotherapy, but no allogeneic HSCT, our patient reached complete molecular remission and has been in complete molecular remission for more than 13 months. This report is the first about the long-term use of dasatinib in patients with Ph+ ALL and MRD elevation but hematologic remission during imatinib chemotherapy. In a similar situation, chemotherapy combined with dasatinib instead of allogeneic HSCT could be considered to avoid HSCT-related mortality and morbidity. Clinical trials are needed.

**Key Words** Dasatinib, Philadelphia chromosome, acute lymphoblastic leukemia, complete molecular remission, children

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## INTRODUCTION

Before the availability of tyrosine kinase inhibitors (TKIs), acute lymphoblastic leukemia (ALL) positive for the Philadelphia chromosome (Ph+) was associated with extremely poor outcomes. The introduction of imatinib in combination with chemotherapy dramatically improved the prognosis of patients with Ph+ ALL[1–4]. Hematopoietic stem-cell transplantation (HSCT) can be an important treatment option for patients who respond poorly to imatinib plus chemotherapy. However, HSCT carries a considerable risk of morbidity and even mortality.

In patients with leukemia, minimal residual disease (MRD) has been widely used to monitor response to treatment and to predict subsequent relapse. However, there is no consensus about how to treat children with elevation of *BCR-ABL* transcripts but no evidence of hematologic relapse during chemotherapy combined with imatinib. In such situations, allogeneic HSCT has been reported to overcome resistance to imatinib and relapse[5]. A reasonable option is therefore to treat these patients with a second-generation TKI such as dasatinib, followed by allogeneic HSCT[6–8]. However, the long-term efficacy of dasatinib therapy in this situation has not been reported. Here, we reported the first patient with Ph+ ALL and persistently elevated MRD during imatinib plus intensive chemotherapy in whom the use of dasatinib plus less-intensive chemotherapy without allogeneic HSCT achieved long-term molecular remission.

## CASE DESCRIPTION

A 9-year-old boy originally showed symptoms of fever and bleeding gums for 7 days. Physical examination demonstrated pale conjunctivae and hepatosplenomegaly. An elevated leucocyte count ($112.3\times10^9$/L), with anemia (hemoglobin 5.9 g/dL) and thrombocytopenia ($13\times10^9$/L), was

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noted in peripheral blood. The diagnosis of B-precursor ALL was made after bone marrow examination. Cytogenetic study revealed a complex chromosomal abnormality with 46,XY, t(9;22)(q34;q11.2), der(6)t(6;?)(p25;?)[10]/46,XY, and der(17)t(17;?)(q25;?)[2]/46,XY[3]. In addition, molecular analysis detected the e1a2 *BCR-ABL* fusion transcript.

Upon the diagnosis of Ph+ ALL, the boy received a combination of intensive chemotherapy and imatinib per the Japan Adult Leukemia Study Group ALL202 protocol[9]. Imatinib was administered, in combination with other drugs, at a dose of 340 mg/m$^2$ daily after induction therapy. Quantification of the e1a2 *BCR-ABL* transcript in bone marrow samples by real-time quantitative polymerase chain reaction with TaqMan probes (Roche Molecular Systems, Pleasanton, CA, U.S.A.) was used to detect MRD[10].

After 8 months of treatment, quantification of e1a2 *BCR-ABL* transcripts in a bone marrow sample reached a 3.5 log reduction compared with the median pretreatment level. However, 3 months later, e1a2 *BCR-ABL* transcripts were elevated at a 3.0 log reduction, and 6 months later, were further elevated at a 2.2 log reduction (Figure 1). There was no evidence of hematologic relapse. To detect imatinib-resistant mutations, direct sequencing of the *BCR-ABL* tyrosine kinase domain in a bone marrow sample was performed, demonstrating a wild-type *BCR-ABL* tyrosine kinase domain without any mutation.

No suitable donor or cord blood was available for HSCT, and we decided to replace the imatinib with dasatinib 60 mg/m$^2$ daily. To avoid toxicity (given the intensive treatment already received by the patient), only low-dose methotrexate (40 mg/m$^2$ weekly) and 6-mercaptopurine (50 mg/m$^2$ daily) were given concomitantly with the dasatinib.

By 5 months after the start of dasatinib treatment, the level of e1a2 *BCR-ABL* transcripts reached a 4.3 log reduction, and complete molecular remission (>5 log reduction) was subsequently achieved. With continuous dasatinib plus chemotherapy, but no allogeneic HSCT, the patient has been in complete molecular remission for more than 13 months (Figure 1). No serious adverse events were encountered. The changes in MRD levels before and after dasatinib are presented in Figure 1.

## DISCUSSION

A significant correlation of MRD elevation with subsequent relapse has been demonstrated in patients with Ph+ ALL[5,11–14]. Yanada *et al.*[5] reported that 29 patients with Ph+ ALL showed MRD elevation during hematologic complete remission. Of those 29 patients, 12 of the 13 who had not undergone allogeneic HSCT after MRD elevation experienced earlier relapse (median: 2 months from MRD elevation to relapse). In contrast, important concerns have been expressed that MRD might be oversensitive and without clinical relevance. Imatinib therapy was therefore continued in our present patient when the first elevation in MRD was detected at 1 year after diagnosis. When, 3 months later, the elevation in e1a2 *BCR-ABL* transcripts continued (to a 2.2 log reduction from a 3.0 log reduction), the two successively elevated MRD levels caused us to worry that relapse might occur soon—possibly even before the next MRD follow-up—and relapse usually signifies a dismal prognosis. Beneficial effects of dasatinib have been demonstrated even in Ph+ ALL patients without imatinib-resistant mutations[15,16]. The switch from imatinib to dasatinib was therefore a reasonable option for our patient's specific circumstances.

There is no consensus on how to treat Ph+ ALL patients with MRD elevation but hematologic remission during treatment with imatinib combined with chemotherapy. The long-term efficacy of dasatinib therapy in such a situation is uncertain. Because allogeneic HSCT has been reported to overcome resistance to imatinib in these patients[5], physicians might prefer to perform allogeneic HSCT, considering dasatinib only as a bridge to HSCT. Because morbidity and even mortality are associated with allogeneic HSCT[17,18], an evaluation of whether dasatinib combined with chemotherapy can replace allogeneic HSCT in patients with Ph+ ALL who have MRD elevation during imatinib therapy is worth study. Our patient never underwent HSCT. With dasatinib plus less-intensive chemotherapy, complete molecular remission was successfully achieved and has been maintained for more than 13 months. Although only constituting a case report, the promising results in our

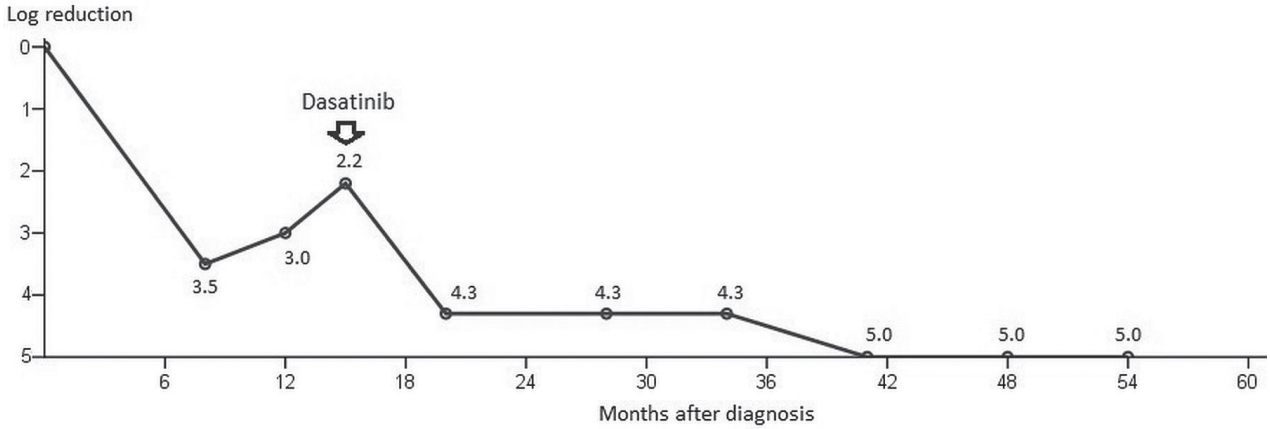


**FIGURE 1** Changes of *BCR-ABL* transcripts before and after start of dasatinib.

patient could represent encouragement to perform trials of the long-term use of dasatinib plus chemotherapy to replace allogeneic HSCT in such patients so as to avoid HSCT-related side effects.

As single agents, TKIs have limited activity against Ph+ ALL, and they are therefore administered in combination with other chemotherapeutic drugs. However, no consensus on the chemotherapy backbone for children with Ph+ ALL has been reached. How intensive a backbone is needed is not known. The optimal efficacy of TKI therapy might be compromised if the tumouricidal capability of immune cells is reduced because of intensive chemotherapy[19]. Results of imatinib plus relatively little chemotherapy have been encouraging in elderly adults with Ph+ ALL, and better outcomes in children with Ph+ ALL have been reported[1,2]. Because our patient had been heavily pretreated, he was given relatively less-intensive chemotherapy (low-dose methotrexate and 6-mercaptopurine) with the dasatinib given at the time of MRD elevation. His very good response resulted in complete molecular remission. He has been doing well and enjoys a good quality of life.

The efficacy of the TKIs probably plays the major role, with other chemotherapeutic agents acting as adjuvants, in the treatment of childhood Ph+ ALL. Dasatinib plus less-intensive chemotherapy could therefore be a reasonable choice of treatment for children with Ph+ ALL who have an unsatisfactory response to initial intensive therapy.

## SUMMARY

This report is the first about the long-term use of dasatinib in a Ph+ ALL patient with MRD elevation but hematologic remission during treatment with imatinib combined with chemotherapy. Using dasatinib plus less-intensive chemotherapy without HSCT, our patient has been doing well, being in complete molecular remission for more than 13 months. Those promising results in this particular setting could be encouragement to perform trials of the long-term use of dasatinib therapy to replace allogeneic HSCT, thus avoiding HSCT-related morbidity and mortality.

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### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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