of acute promyelocytic leukemia, which was seen at breakpoint 15q24 and 17q21. Another balanced translocation between long arm of chromosome 10 and long arm of chromosome 20 was also identified.

This case highlights an unusual case of secondary AML in an adult patient with B-ALL during maintenance chemotherapy, which evolved from a normal karyotype during ALL to a highly complex karyotype as AML developed. It also highlights the importance of performing immunophenotyping at the time of relapse in every case of acute leukemia to identify any change in immunophenotyping or any lineage switch to administer the correct therapy and to analyze minimal residual disease on follow-up.

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REFERENCES

1. Verma D, O'Brien S, Thomas D, et al. Therapy-related acute myelogenous leukemia and myelodysplastic syndrome in patients with acute lymphoblastic leukemia treated with the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimens. Cancer 2009;115:101-6.

2. Morton LM, Dores GM, Tucker MA, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood 2013;121:2996-3004.

3. Kayser S, Döhner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011;117:2137-45.

4. Wu B, Jug R, Luedke C, et al. Lineage switch between B-lymphoblastic leukemia and acute myeloid leukemia intermediated by 'Occult' myelodysplastic neoplasm: two cases of adult patients with evidence of genomic instability and clonal selection by chemotherapy. Am J Clin Pathol 2017;148:136-47.

5. Pagano L, Annino L, Ferrari A, et al. Secondary haematological neoplasm after treatment of adult acute lymphoblastic leukemia: analysis of 1170 adult ALL patients enrolled in the GIMEMA trials. Gruppo Italiano Malattie Ematologiche Maligne dell’Adulto. Br J Haematol 1998;100:669-76.

6. Tavernier E, Le QH, de Botton S, et al. Secondary or concomitant neoplasms among adults diagnosed with acute lymphoblastic leukemia and treated according to the LALA-87 and LALA-94 trials. Cancer 2007;110:2747-55.

7. Grosicki S, Barchnicka A, Bodzenta E, Haus O, Jaśkowiec A. Secondary acute myeloid leukemia (sAML) immediately after intensive chemotherapy of acute lymphoblastic leukemia (ALL). J Leuk 2013;1:100102.

Efficacy of ponatinib prior to and after allogeneic hematopoietic stem cell transplantation in an adolescent with chronic myeloid leukemia in blast phase

TO THE EDITOR: BCR-ABL1 kinase domain mutations confer resistance to imatinib in chronic myeloid leukemia (CML) patients. Ponatinib is the only tyrosine kinase inhibitor (TKI) able to eradicate leukemic cells harboring the T315I mutation, which replaces a threonine with isoleucine within the ATP binding site of the tyrosine kinase protein [1]. However, the drug is currently only approved for adult CML patients, with limited reports of its use in children and adolescents. Here, we report on the efficacy of ponatinib before and after allogeneic hematopoietic stem cell transplantation (HSTT) in an adolescent patient with blast phase chronic myeloid leukemia (CML) who relapsed with the T315I mutation.

A 16-year-old male patient was diagnosed with B lymphoid blast phase (BP) CML and received initial treatment with prednisolone combined with imatinib at 600 mg/day for 4 weeks. A follow-up bone marrow (BM) study showed complete hematologic response (CHR) with major cytogenetic response. While maintaining imatinib with the aim of undergoing allogeneic HSCT, the patient relapsed to accelerated phase (AP) 4 months after achieving initial CHR.

Complete blood count at the time of AP relapse showed a white blood cell count of 11.77×10⁹/L (8% blasts), hemoglobin 8.6 g/dL and platelet count of 82×10⁹/L, while the BM showed 18% blasts (Fig. 1). The patient progressed to B lymphoid BP again one month later. Molecular studies for BCR-ABL1 kinase domain mutations done at the time of AP relapse showed the T315I mutation. As ponatinib, the only TKI with efficacy against CML cells with the T315I mutation, is not approved for children and adolescents, the patient received a 4-drug reinduction regimen consisting of vincristine, daunorubicin, asparaginase and dexamethasone, as well as intrathecal chemotherapy; this resulted in second CHR, although the BCR-ABL1 transcript value, reported as the ratio of BCR-ABL1 to ABL1 measured by real-time quantitative reverse transcription-polymerase
Fig. 1. Bone marrow findings at the time of AP relapse showed 18% leukemic blasts (arrow) (Wright-Giemsa stain, ×1,000).

Fig. 2. Changes in the ratio of \( \text{BCR-ABL1/ABL1} \) RQ-RT-PCR value for the patient from diagnosis to last follow-up. All values were obtained from peripheral blood, except for (*) which was obtained from bone marrow. Abbreviations: BP, blast phase; CHR, complete hematologic response; MSD PBSCT, matched sibling donor peripheral blood stem cell transplantation.

Although ponatinib is effective in CML patients resistant to first-line TKI therapy, the drug also has the potential for serious side effects. A phase 2 study of ponatinib in adult patients with Ph+ leukemias with long-term follow-up reported that the most common adverse events in chronic phase CML patients were rash, abdominal pain and thrombocytopenia, while serious adverse events included pancreatitis, atrial fibrillation, pneumonia and angina pectoris [8]. The majority of these side effects occurred within 3 months of starting ponatinib [9]. Perhaps the most distinct complication of ponatinib therapy is arterial occlusive events (AOEs), and the landmark phase 2 study reported a 25% cumulative incidence of AOE[s at 5 years, with a median time to onset of 13.4 months [8]. The risk for AOE[s is likely related to the dose of ponatinib, underscoring the need to treat with the minimum effective dose [10]. Our patient showed skin complications, including facial rash and peripheral limb erythema, on restarting ponatinib after post-HSCT molecular relapse. We subsequently decreased the ponatinib dose once the \( \text{BCR-ABL1} \) transcript reverted to undetectable status, and he has since remained free of possible drug-related side effects. The range and severity of ponatinib-related adverse events may differ in children compared with adults, and currently ongoing clinical trials of ponatinib therapy in the pediatric setting may conclude upon the appropriate dose, safety and efficacy of this drug.

The optimum duration of prophylactic TKI therapy for CML patients post-allogeneic HSCT remains unclear. One recent study on adult patients with Ph+ leukemias reported a median duration of post-HSCT TKI therapy of 16 months [11]. Specifically regarding ponatinib, one study on an adult patient with T315I mutation (+) BP CML described prophylactic therapy for more than 1 year after HSCT [12]. Studies
on the duration of TKI therapy necessary for patients who show molecular relapse post-HSCT are also few. One adult study showed that 4 out of 10 CML patients continued to show complete molecular response after stopping imatinib therapy initiated for molecular or cytogenetic relapse after HSCT; the median duration of TKI therapy was 269 days in the 4 patients [13]. Maintaining deep molecular remission for at least 2 years was a criterion used in studies on imatinib cessation in both adult and pediatric CML patients [14, 15]. A similar prerequisite may be considered for stopping TKI therapy administered for post-HSCT relapse, although patients who have received allogeneic HSCT, unlike transplant-naive patients treated with TKI only, may be aided by the immunologic effects of the graft.

In summary, our case study adds to the limited literature on children and adolescents with T315I mutation (+) CML treated with ponatinib. The TKI was able to significantly decrease the BCR-ABL1 transcript load within a short time span in a BP patient in second CHR prior to transplant, and also induced and maintained remission for molecular relapse post-transplant. Further studies on the optimum dose of the TKI for children and adolescents may allow for safer treatment with this drug in rare Ph+ pediatric leukemias.

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REFERENCES
1. O’Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell 2009;16:401-12.
2. Nickel RS, Daves M, Keller F. Treatment of an adolescent with chronic myeloid leukemia and the T315I mutation with ponatinib. Pediatr Blood Cancer 2015;62:2050-1.
3. Yamamoto M, Hori T, Igarashi K, Shimada H, Tsutsumi H. Response to ponatinib before hematopoietic stem cell transplantation in a child with relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia. Pediatr Int 2018;60:85-7.
4. Gruner SE, Sayeed H, Suarez-Ferguson L, et al. Ponatinib use in two pediatric patients with relapsed Ph+ ALL with ABL1 kinase domain mutations. Pediatr Hematol Oncol 2019;36:514-9.
5. Aksu T, Ünal Ş, Gümrük F. The remarkable response to ponatinib therapy in a child with blastic phase of chronic myeloid leukemia. Turk J Pediatr 2020;62:479-81.
6. Rossoff J, Huynh V, Rau RE, et al. Experience with ponatinib in pediatric patients with leukemia. Br J Haematol 2020;189:363-8.
7. Millot F, Suttrop M, Versluis AB, et al. Ponatinib in childhood Philadelphia chromosome-positive leukaemias: an international registry of childhood chronic myeloid leukaemia study. Eur J Cancer 2020;136:107-12.
8. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukaemias: final 5-year results of the phase 2 PACE trial. Blood 2018;132:393-404.
9. Le Coutre PD, Kim DW, Pinilla-Ibarz J, et al. Ponatinib in heavily pretreated patients with chronic phase chronic myeloid leukaemia (CPCML): management of adverse events (AEs). Blood (ASH Annual Meeting Abstract) 2013;122(Suppl):abstr 1496.
10. Dorer DJ, Knickerbocker RK, Baccarani M, et al. Impact of dose intensity of ponatinib on selected adverse events: multivariate
analyses from a pooled population of clinical trial patients. Leuk Res 2016;48:84-91.
11. DeFilipp Z, Langston AA, Chen Z, et al. Does post-transplant maintenance therapy with tyrosine kinase inhibitors improve outcomes of patients with high-risk Philadelphia chromosome-positive leukemia? Clin Lymphoma Myeloma Leuk 2016;16:466-71.
12. Sasaki H, Mitani S, Kusumoto S, et al. Pre- and post-transplant ponatinib for a patient with acute megakaryoblastic blast phase chronic myeloid leukemia with T315I mutation who underwent allogeneic hematopoietic stem cell transplantation. Int J Hematol 2019;110:119-23.
13. Hess G, Banjes D, Siegert W, et al. Sustained complete molecular remissions after treatment with imatinib-mesylate in patients with failure after allogeneic stem cell transplantation for chronic myelogenous leukemia: results of a prospective phase II open-label multicenter study. J Clin Oncol 2005;23:7583-93.
14. Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010;11:1029-35.
15. de Bruijn CMA, Millot F, Suttorp M, et al. Discontinuation of imatinib in children with chronic myeloid leukaemia in sustained deep molecular remission: results of the STOP IMAPED study. Br J Haematol 2019;185:718-24.

A case of e1a2 (minor, P190) BCR-ABL1-positive chronic myeloid leukemia in Korea

TO THE EDITOR: Minor BCR-ABL1-positive chronic myeloid leukemia (CML) is a very rare subtype of CML, with only 1-2% of patients with CML exhibiting this fusion gene as a sole rearrangement [1]. Amongst the several reported cases in literature, and to the best of our knowledge, only one case has been reported in Korea so far [2]. In this letter, we report a Korean patient diagnosed with minor BCR-ABL1-positive CML.

An 81-year-old male with a history of hypertension and dyslipidemia was referred to our hospital because of marked leukocytosis. The complete blood count (CBC) at referral indicated anemia, leukocytosis, and thrombocytopenia, with a hemoglobin (Hb) level of 7.5 g/dL, white blood cell (WBC) count of 37.59×10^9/L, and a platelet count of 89×10^9/L. The differential counts of WBC were myelocytes 1%, metamyelocytes 2%, band neutrophils 13%, neutrophils 45%, eosinophils 2%, basophils 6%, lymphocytes 12%, and monocytes 19% (Fig. 1). Bone marrow (BM) biopsy and related cytogenetic studies were performed; bone marrow biopsy showed hypercellularity, with an estimated cellularity of 70-90% (Fig. 2) with granulocytic proliferation. Additionally, the number of megakaryocytes and dwarf megakaryocytes had increased (Fig. 3). Approximately 5.3% of all nucleated cells (ANCs) were counted as blasts, whereas the population co-expressing CD34(+), CD117(+), and myeloperoxidase corresponding to myeloblasts, was 2.28% of the total cells observed using flow cytometry (FCM). Pseudo-Gaucher cells were not observed. Monocytes accounted for 17.1% of the ANCs, consistent with the FCM results of 17.4%. Conventional chromosome analysis using BM cells exhibited 46,XY,t(9;22)(q34;q11.2)[20] (Fig. 4). Reverse transcriptase-polymerase chain reaction (RT-PCR) showed a minor (P190) BCR-ABL1 transcript of the e1a2 type (Fig. 5). No major (P210) or micro (P230) BCR-ABL1 transcripts were detected. Therefore, the patient was diagnosed with minor BCR-ABL1-positive CML in chronic phase.

The Philadelphia chromosome, resulting from the chro-

Fig. 1. A peripheral blood smear showing leukocytosis with monocytes (blue arrow), basophilia (red arrow) and left shift (yellow arrow) (white blood cell count 37.59×10^9/L with 0.19 monocytes and 0.04 basophils, Wright-Giemsa stain, ×400).
Fig. 2. Bone marrow biopsy showing hypercellularity (estimated cellularity of 70-90%, Hematoxylin & Eosin stain, ×200).