Ponatinib Induces a Persistent Molecular Response and Graft-versus-Host Disease/Graft-versus-Leukemia Effect in a Patient with Philadelphia-Positive Acute Lymphoblastic Leukemia with a T315I Mutation following Early Relapse after Allogeneic Transplant

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Abstract
We describe the case of a patient with a Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) treated with dasatinib plus steroids as the first-line therapy who achieved a molecular complete remission and then underwent a matched, unrelated donor allogeneic transplant. Five months after the transplant, he experienced a disease relapse with an T315I mutation, which was resistant to salvage treatment. Ponatinib, a third-generation TKI with activity against the T315I-resistant mutation, was then administered as the second-line therapy. The patient achieved a molecular remission and a graft-versus-host disease/graft-versus-leukemia effect, which was associated with a significant improvement in his general condition and the resolution of his symptoms.

Key Words
Acute lymphoblastic leukemia · Philadelphia chromosome · Allogeneic transplant · Ponatinib · T315I mutation · Graft-versus-host disease · Graft-versus-leukemia effect · Thyroid dysfunction

D.R. and F.M. contributed equally to this work.

Established Facts
- Ponatinib is a highly effective treatment for Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) with T315I mutation, and is well tolerated.

Novel Insights
- Ponatinib as a single-agent treatment is able to determine the molecular complete response in Ph+ ALL with T315I mutation after early relapse following allogeneic stem cell transplantation, and can induce a graft-versus-host disease/graft-versus-leukemia effect.
Ponatinib in a Patient with Ph+ ALL with a T315I Mutation

Case Report

We present the case of a 37-year-old man diagnosed with Ph+ ALL in May 2014. At diagnosis, the patient presented with a white blood cell count of 17 × 10⁹/L with 80% lymphoid blasts in a peripheral blood smear and severe pain due to the presence of multiple pathologic areas in the pelvic bones. A bone marrow (BM) aspiration confirmed the diagnosis, showing the presence of a B-common immunophenotype and expression of the BCR/ABL1 p190 fusion protein. Cerebrospinal fluid analysis by flow cytometry was negative for central nervous system involvement. On May 21, 2014, after 1 week of steroid pretreatment without a response, we started a ‘chemo-free’ induction program with dasatinib 140 mg/daily plus prednisone, associated with the intrathecal administration of methotrexate as a prophylaxis, which resulted in a rapid hematologic CR and negative minimal residual disease (MRD) on day 94 as shown by molecular assessment. On September 19, 2014, the patient underwent an HSCT from a matched, unrelated donor after a myeloablative conditioning regimen that included thioTEPA, busulfan, fludarabine and antithymocyte globulin. The graft-versus-host disease (GVHD) prophylaxis consisted of the classical association of cyclosporine and methotrexate. Neither acute GVHD nor other significant clinical complications were observed after transplant and the chimerism detected on day 100 was of full-donor origin. In February 2015, the patient experienced a hematological relapse with T315I mutation. Considering the patient’s severe clinical conditions, we immediately started salvage therapy with mitoxantrone and high-dose cytarabine, resulting in resistant disease. For this reason and once the information about T315I was acquired, on April 15, 2015, we started ponatinib at the standard dose of 45 mg/daily. The BM remission on days 30 and 60 showed an impressive decrease of MRD by molecular assessment (0.047 and 0%, respectively) and a full-donor chimerism in both checks. An early grade 2 neutropenia (according to common toxicity criteria, version 4.02) was easily managed with filgrastim administration. Donor lymphocyte infusion was not performed due to donor refusal. After 1 month from starting ponatinib treatment, we observed the occurrence of a psoriasis-like rash without itching on the torso and legs, initially interpreted as ponatinib skin toxicity. However, the rash showed progressive worsening until the diagnosis of extensive chronic GVHD was performed. In August, the patient started 1 mg/kg prednisone and extracorporeal photopheresis, which was continued until November, resulting in a complete regression of cutaneous GVHD. In December, we started an antifungal treatment with a standard dose of voriconazole for pulmonary aspergillosis. Ponatinib was temporarily suspended and then resumed at a daily dose of 15 mg considering the well-known interactions between azoles and TKIs on P450 cytochrome. Moreover, in January 2016, the patient experienced the occurrence of palpitations associated with bilateral leg edema. Considering the well-known cardiovascular toxicity of ponatinib, a comprehensive cardiologic and metabolic evaluation was planned: electrocardiography confirmed the presence of extrasystoles in the absence of further significant rhythm abnormalities, whereas echocardiography was negative for structural dysfunctions. From the results of blood examinations, a diagnosis of hypothyroidism in the absence of antithyroid antibodies was made. All signs and symptoms of the patients completely resolved with hormonal substitution treatment. BM evaluations after 3, 6, 10 and 13 months (the last molecular check was in May 2016) from the start of ponatinib treatment were all MRD negative (fig. 1).
Discussion

Here we have reported a case of early posttransplant relapsed Ph+ ALL with T315I mutation that achieved a persistent CR with negative MRD after treatment with single-agent ponatinib. There are interesting aspects to highlight from the case. First of all is the impressively fast, deep and persistent molecular response obtained by ponatinib in a patient with very little therapeutic options, even though promising results have previously been obtained by the use of blinatumomab [12] and of chimeric antigen receptor T cells [13]. Our case suggests for the first time that ponatinib treatment could also be effective in this challenging population of patients with an early T315I-positive and chemoresistant relapse after HSCT. However, further studies are warranted to confirm this finding. A second aspect is that the efficacy of ponatinib treatment could be related not only to a direct antileukemic effect, but also to its ability to promote an indirect immunologic graft-versus-leukemia (GVL) effect. In fact, our patient experienced a skin GVHD only after starting ponatinib treatment, whereas no occurrence of GVHD was observed after the transplant. In addition, side effects of ponatinib could be related not only to off-target action on kinases, but also to an immunomodulation, as suggested by the frequent observation of skin reactions during treatment. We could hypothesize that ponatinib induced a GVHD/GVL in our patient, considering that he did not experience a GVHD after transplant. However, the mechanism by which this effect occurs is absolutely unclear and there are no data in the medical literature relating to this interesting issue. However, we know from registered studies that the approved daily dose of 45 mg of ponatinib largely exceeds the pharmacokinetic requirements for inhibiting T315I ABL and suppressing the growth of other mutant clones [14]. This aspect could be supported by the persistent molecular remission observed in our patient, also during the drug reduction to a daily dose of 15 mg. Therefore, we could hypothesize that the unexpected GVHD/GVL is the result of an ‘off-target’ effect due to the overexposure to ponatinib. Finally, our case shows that a comprehensive evaluation of adverse events during ponatinib treatment is highly recommended. Our patient presented cardiologic toxicity not directly related to the well-known thromboembolic risk of ponatinib administration [15], but to a thyroid dysfunction. A thyroid dysfunction is a common adverse event described during the treatment of chronic myeloid leukemia with second-generation TKIs [16], and registered studies report a thyroid dysfunction in about 3% of patients treated with ponatinib. However, the pathophysiologic mechanism remains elusive.

![Fig. 1. Monitoring of BM levels (BCR-ABL/ABL, %) during the clinical progress of the patient. PDN = Prednisone; HAM = high-dose cytarabine, mitoxantrone; d = day; m = months.](image-url)
In conclusion, our case shows that single-agent ponatinib was highly effective in the treatment of a patient with Ph+ ALL with early relapse after HSCT, suggesting significant antileukemic action achieved by directly overcoming the resistance induced by the T315I mutation and indirectly inducing a GVL effect. Ponatinib treatment is considered safe overall but a careful evaluation of adverse events is required.

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Disclosure Statement

The authors declare no financial or other potential conflicts of interest.

References