Clinical activity of ponatinib in patients with chronic myeloid leukemia in chronic phase with e1a2 transcripts

The two major types of transcripts[1] of the BCR-ABL1 oncoprotein are b2a2 (e13a2) and b3a2 (e14a2). These transcripts are observed in over 95% of patients with chronic myeloid leukemia in chronic phase (CML-CP) at the time of initial presentation. Very rarely (<1%), CML patients are seen harboring e1a2 transcripts.[2,3] Patients with e1a2 transcripts exhibit a p190 Kda oncoprotein, aggressive disease course, present with monocytosis, respond poorly to therapy with tyrosine kinase inhibitors (TKI), and have a higher risk of transformation to accelerated and blast phase.[4-6] Mechanistically, P190 BCR-ABL induces lymphoid transformation in the B-lymphoid cells at a faster rate than P210 or P230 BCR-ABL. However, all the three variants of BCR-ABL[6] demonstrate the same frequency of myeloid transformations. Furthermore, we have previously reported that patients with CML and the rare e1a2 transcripts have poor response to therapy with TKI.[5] Ponatinib was not evaluated in that report.[5] Another study of 33 patients with relapsed Ph$^+$ ALL and e1a2 transcripts (p190) has shown that emergence of ABL kinase domain mutations (T315I and Y253H) while on therapy with TKI was associated with the lack of efficacy of TKI in these patients.[7] Ponatinib is a novel TKI agent and has recently been approved for treatment of relapsed refractory CML.[8] Ponatinib has demonstrated efficacy in patients with T315I and other mutations. We report on our experience of 2 patients with relapsed refractory CML in chronic phase (CML-CP) with e1a2 transcripts who were treated with ponatinib (Table 1).

Patient A was a 51-year old man who presented five years after the initial diagnosis of CML-CP. He had failed 4 prior therapies (interferon, imatinib, dasatinib, bosutinib). Prior to therapy with ponatinib he had splenomegaly (10 cm) and was in complete hematologic remission (CHR) but had never achieved any cytogenetic response. He did not exhibit any ABL kinase domain mutations. He was treated with a daily dose of 15 mg ponatinib. Three weeks after starting ponatinib there was a reduction in spleen size to being minimally palpable but he developed grade 3 thrombocytopenia requiring interruption of treatment. He had no other toxicities attributable to ponatinib. He did not achieve any cytogenetic response and progressed to lymphoid blast phase after 21 months of treatment with ponatinib. Subsequently, he received therapy with hyper-CVAD with rituximab and nilotinib followed by matched sibling donor allogeneic stem cell transplant and died from hepatic dysfunction due to infection from hepatitis C virus.

Patient B was a 62-year man with a diagnosis of CML seven years previously. He had failed 4 prior TKI therapies (imatinib, dasatinib, nilotinib, DCC-2036). Prior to starting on ponatinib he was in CHR but had never had any documented cytogenetic response to his previous therapies. He also exhibited T315I and E543G mutations. He was treated with ponatinib 45 mg daily. The patient developed grade 3 elevation of liver enzymes leading to interruption of ponatinib. Treatment was re-started at a dose of 45 mg after it was determined that the hepatotoxicity was due to therapy with niacin for hypertriglyceridemia. The patient maintained adequate peripheral blood counts and did not require any additional treatment interruptions. He did not have any ponatinib-related toxicity. The patient achieved a minor cytogenetic response three months after starting therapy; therapy was maintained for 27 months.

CML-CP with e1a2 rearrangement is a rare condition associated with a poor outcome.[5] To our knowledge, this is the first report of patients with CML-CP with e1a2 treated with ponatinib in the literature. Ponatinib has excellent response rates in most of the CML patients treated who are refractory to multiple TKI.[8]

Experience with ponatinib in CML patients with e1a2 is limited due to the rarity of this entity. However, this brief experience suggests that, in addition to the previously reported poor outcome with other TKI, ponatinib also might not be very effective in patients with CML-CP with e1a2 transcripts. Patient A did not achieve any cytogenetic response and progressed to blast phase (although treated only at 15 mg daily in phase 1) and Patient B had a cytogenetic response, albeit only minor (which might be considered of clinical benefit).[9] Interestingly, Patient B had T315I mutation which is highly sensitive to ponatinib. In the pivotal phase I study of ponatinib in refractory Ph$^+$ leukemia, 12 CML patients in chronic phase with T315I mutation were treated and 11 of these (92%) achieved a major cytogenetic response.[8] In the phase II PACE trial, 70% of patients with T315I treated in chronic phase achieved a major cytogenetic response, a higher rate than that of patients with any other mutation (57%) or no mutation (49%).[10] Therefore, it is possible that the presence of e1a2 transcripts overshadowed the efficacy of ponatinib on the T315I mutation. Still, it has to be emphasized that this patient had not achieved a cytogenetic response with any prior TKI and this minor response is his

Table 1. Summary of the 2 patients on ponatinib.

	Patient A	Patient B
Transcript at diagnosis.	e1a2	e1a2
Age at start ponatinib (yrs)	51	62
Number of prior TKI	3	4
Interferon	Yes	No
Imatinib	Yes	Yes
Dasatinib	Yes	Yes
Nilotinib	No	Yes
Bosutinib	Yes	No
DCC-2036	No	Yes
PFS (mo)	21.4	27+
Months on ponatinib (up to Last follow up)	21	27+
Follow-up time (mo)	34	27+
OS (mo)	34.6	27+
Survival status	Dead	Alive
Diagnosis at start	CML-CP	CML-CP
Reason off study	Disease progression	Treatment ongoing
Starting ponatinib dose	15 mg	45 mg
Ponatinib treatment interruptions	Yes	Yes
Reason for interruption	Thrombocytopenia	Grade 3 elevation of bilirubin
Dose reduction	Yes, up to 8 mg after the second time it was held	No

best response ever. The mechanisms of ponatinib or other TKI that may have inferior clinical activity in patients with e1a2 transcripts (CML-CP or in Ph+ acute lymphoblastic leukemia) are unclear. Thus, based on the available, albeit limited, information, patients with CML and e1a2 transcripts should be considered as a high-risk group and should be evaluated for stem cell transplantation (SCT) early in the course of the disease.

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References

1. Langabeer SE. Is the BCR-ABL1 transcript type in chronic myeloid leukaemia relevant? Med Oncol. 2013;30(2):508.
2. Melo JV. BCR-ABL gene variants. Baillieres Clin Haematol. 1997;10(2):203-22.
3. Jones D, Luthra R, Cortes J, Thomas D, O'Brien S, Bueso-Ramos C, et al. BCR-ABL fusion transcript types and levels and their interaction with secondary genetic changes in determining the phenotype of Philadelphia chromosome-positive leukemias. Blood. 2008;112 (13):5190-2.
4. Ohsaka A, Shiina S, Kobayashi M, Kudo H, Kawaguchi R. Philadelphia chromosome-positive chronic myeloid leukemia expressing p190(BCR-ABL). Intern Med. 2002;41(12):1183-7.
5. Verma D, Kantarjian HM, Jones D, Luthra R, Borthakur G, Verstovsek S, et al. Chronic myeloid leukemia (CML) with P190 BCR-ABL: analysis of characteristics, outcomes, and prognostic significance. Blood. 2009;114(11):2232-5.
6. Li S, Ilaria RL Jr, Million RP, Daley GQ, Van Etten RA. The P190, P210, and P230 forms of the BCR/ABL oncogene induce a similar chronic myeloid leukemia-like syndrome in mice but have different lymphoid leukemogenic activity. J Exp Med. 1999;189(9):1399-412.
7. Jones D, Thomas D, Yin CC, O'Brien S, Cortes JE, Jabbour E, et al. Kinase domain point mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia emerge after therapy with BCR-ABL kinase inhibitors. Cancer. 2008;113(5):985-94.
8. Cortes JE, Kantarjian H, Shah NP, Bixby D, Mauro MJ, Flinn I, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med. 2012;367(22):2075-88.
9. Cortes J, Quintas-Cardama A, Jabbour E, O'Brien S, Verstovsek S, Borthakur G, et al. The clinical significance of achieving different levels of cytogenetic response in patients with chronic phase chronic myeloid leukemia after failure to front-line therapy: is complete cytogenetic response the only desirable endpoint? Clin Lymphoma Myeloma Leuk. 2011;11(5):421-6.
10. Cortes JE, Kim D-W, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, et al. A Pivotal Phase 2 Trial of Ponatinib in Patients with Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL) Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 12-Month Follow-up of the PACE Trial. ASH Annual Meeting Abstracts. 2012;120(21):163.