

Ponatinib Before and after Allogeneic Stem Cell Transplantation for Ph⁺ Acute Lymphoblastic Leukemia or Lymphoid Blast Crisis of Chronic Myelogenous Leukemia: A Single Center Experience

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Abstract

Role of Ponatinib, given as bridge to transplantation or at relapse after aSCT in patients affected by Philadelphia acute lymphoblastic leukemia (ALL) or lymphoid BC-CML is also not well understood.

We report a retrospective analysis that included allograft recipients with blast phase chronic myeloid leukemia or (Ph⁺) acute lymphoblastic leukemia who had received ponatinib before and/or after aSCT. Patients were all assessed for BCR/ABL mutations before ponatinib administration and after relapse: only two patients showed compound mutation.

At a median of 21 months 6 out of 7 patients have died from disease progression and one patient died from septic shock after aSCT. In our experience ponatinib, given as bridge to transplantation or at relapse after aSCT, is useful to obtain a rapid hematological response in almost all patients and occasionally morphological and molecular response, but unfortunately they were short-lived.

Keywords: Acute lymphoblastic leukemia; Chronic myeloid leukemia; Allogeneic stem cell transplantation; Ponatinib

Introduction

Philadelphia (Ph⁺) chromosome is one of the most frequent cytogenetic abnormalities in adult acute lymphoblastic leukemia (ALL) and it is historically considered as a poor prognosis factor also before and after allogeneic stem cell transplantation (aSCT). BCR-ABL1-directed tyrosine kinase inhibitors (TKIs), including imatinib mesylate and second generation TKIs have been used as single agents or in combination with classical chemotherapeutic agents generating excellent results particularly in the induction phase of Ph+ALL [1,2]. Despite these encouraging results, Ph+ ALL or lymphoid blast crisis (L-BC) of chronic myelogenous leukemia (CML) still remains a major indication for aSCT due to the high rate of leukemia relapse. Genomic instability and the high propensity to develop BCR/ABL mutations either related to disease itself or the selective pressure of TKIs; confer resistance to TKIs and chemotherapy and dismal prognosis at relapse [3]. Ponatinib is a pan-BCR-ABL tyrosine kinase inhibitor (TKI) capable of inhibiting BCR-ABL with the gatekeeper T315I kinase domain mutation, known to be one of the leading cause for many resistant or relapsed cases of CML and Ph+ALL. Little is known on the use of ponatinib as bridge to transplantation or at relapse in Ph+ ALL or lymphoid BC harboring T315I mutation and this analysis wants described the role of the drug in this setting of patients observed in our department.

Materials and Methods

The BCR-ABL kinase domain was amplified by nested-RT-PCR using specific fusion primers. The resulting amplicons were analyzed by ultra-deep sequencing on a Roche GS Junior next generation sequencer as previously described [4] Amplicon Variant Analyzer (version 2.7; 454-Life Sciences) was used to align reads to the reference ABL sequence (GenBank accession no.X16416) and to calculate variant frequencies. Clonal analysis was performed by visual inspection of read clusters harboring the relevant mutations. Sequencing runs were designed to ensure a lower detection limit of 1% sensitivity in all the samples, the target sequence coverage ranging from 3990 to 6554 independent reads for each nucleotide position.

Results

We report our experience in seven patients with Ph+ALL or lymphoid BC-CML treated with ponatinib before and/or after aSCT. Patients were all assessed for BCR/ABL mutations before ponatinib administration and in 5 out of 7 patients at relapse on ponatinib.

Five patients had Ph+ ALL and 2 patients had lymphoid BC-CML, 4 were males and 3 females, with a median age of 50 years (range 32-63). Four patients had oncoprotein p190 and three patients had p210 as molecular marker of disease. Mutation analysis prior to ponatinib was negative in 4 patients and in 3 patients was positive for T315I mutation. Three patients were treated with ponatinib before aSCT and 5 patients received the drug after aSCT. Median dose of ponatinib was 45 mg (range 15-45) daily prior to aSCT and 15 mg (range 15-30) after aSCT respectively. (Patient characteristics were resumed in Table 1)

Characteristics	Number of Patients
Median age	50 years (range 32-65)
Male	4
Female	3
LLA Ph positive	5
BC CML	2
P190	4
p210	3
Presence of T315I mutation	4 (Negative) 3 (Positive)
Ponatinib Before SCT	3
After SCT	5 (1 patient received before and after)
Ponatinib as second line therapy	3
Third line therapy	3
Forth line therapy	1
Best response to Ponatinib	3 Haematological Remission 1 Complete Remission
	1 Molecular Remission 1 No response
	1 Not evaluable

Table 1: Patient Characteristics

Case 1

A 32 year old male affected by Ph+ ALL received induction therapy with imatinib achieving complete remission (CR) followed by consolidation chemotherapy and aSCT from his HLA identical sister in morphological CR after myeloablative conditioning regimen including total body irradiation (TBI) and cyclophosphamide. Molecular remission was achieved shortly after SCT but 18 months after aSCT molecular relapse was detected and imatinib was started with no effect followed by overt leukemia relapse within one month. He received conventional chemotherapy with mitoxantrone and cytosine arabinoside with no response. At 21 months after aSCT he then received dasatinib 140 mg/d without response after 1 month of treatment. On a compassionate use basis and without evidence of point mutations of BCR/ABL domain he received ponatinib 45 mg daily followed by donor lymphocyte infusions (DLI). He achieved hematological remission (HR) within 2 weeks and molecular response after 2 months of treatment. Ponatinib was well tolerated with mild thrombocytopenia and skin rash mimicking graft versus host disease (GvHD). Unfortunately 4 months after starting ponatinib a further relapse developed and the patient died two months later.

Case 2

A 49 year old male with Ph+ ALL received induction therapy with dasatinib (GIMEMA LAL1509 protocol) achieving complete molecular remission. At 6 months he developed leukemia relapse without BCR/ABL mutations and he was shifted to ponatinib 45 mg followed shortly by aSCT from his identical brother after myeloablative conditioning regimen.

Three months after aSCT immunosuppression was discontinued for molecular relapse and ponatinib 45 mg was added. He developed skin acute GvHD grade 3 requiring high dose of steroids. Six months after aSCT and after 3 months of ponatinib 45 mg /d the patient unexpectedly developed congestive cardiac failure. Ponatinib was discontinued and resumed few days after the resolution of cardiac complication at the dose of 15 mg. He rapidly obtained the disappearance of BCR/ABL transcript followed by relapse two years after aSCT on ponatinib. The patient died one month later from pneumonia.

Case 3

A 56 years old female with Ph+ALL received induction with imatinib for 90 days (GIMEMA LAL 0409 protocol) followed by aSCT from her HLA identical sister in molecular CR after non myeloablative conditioning regimen. Eight months after aSCT imatinib was restarted for bone marrow relapse after progressive loss of donor chimerism. She then received chemotherapy and five doses of DLI without response. Dasatinib 140 mg/day was then started and she obtained molecular CR lasting 3 years.

Fifty-one months after SCT, the patient was admitted to the hospital with neurological signs of flaccid paralysis and leukemic central nervous system (CNS) involvement was diagnosed together with frank leukemia relapse in bone marrow with a complex karyotype. She started intrathecal chemotherapy and ponatinib at the dose of 45 mg/d. At that time mutation analysis was negative and she rapidly obtained morphological CR. After 2 months she lost response to ponatinib and mutational analysis showed evidence of T315I and E 255V. Sixty months after aSCT the patient relapsed and died two months later.

Case 4

A 56 year old male was diagnosed with Ph+ALL and received dasatinib 140 mg/day (GIMEMA LAL 1509 protocol). He obtained a molecular CR and according to the protocol he received dasatinib until relapse which occurred at 11 months from diagnosis. He was then treated with chemotherapy without achieving remission. Mutation analysis was positive for T315I and ponatinib 45 mg/day was started. After one month of ponatinib the patient achieved molecular remission and received aSCT from his HLA mismatched brother after non myeloablative conditioning regimen. Unfortunately he died at day 22 after aSCT for septic shock.

Case 5

A 63 year old female with Ph+ALL received imatinib at diagnosis. After 5 months leukemia relapse occurred and at that time mutation analysis was positive for T315I and she received Ponatinib 30 mg. On ponatinib she rapidly achieved morphological CR with no evidence of molecular remission. Five months later she received aSCT from a matched unrelated donor after non myeloablative conditioning regimen. Molecular response was achieved after aSCT but 8 months after aSCT leukemia relapse occurred. Ponatinib was reintroduced with a transient hematological remission. Mutation analysis showed T315I, G250R, and Y253H. The patient received conventional chemotherapy and DLI with no evidence of response and she died 17 months after aSCT.

Case 6

A 34 year old female with CML, high Sokal score received nilotinib as first line therapy. Despite a major molecular response (MMR)

obtained at 5 months from diagnosis, she progressed to abrupt lymphoid BC-CML at 6 months from diagnosis. She was then shifted to dasatinib with no response. Mutational analysis detected T315I point mutation and as a bridge to aSCT from a matched unrelated donor she was shifted to ponatinib 15 mg/d. The patient achieved morphological CR after 3 months of ponatinib and she underwent aSCT after myeloablative conditioning regimen. She never achieved a durable remission despite DLI administration and concurrent GVHD. The patient died 12 months after aSCT. Mutation analysis detected T315I mutation and other different leukemic mutated clones.

Case 7

A 43 year old male with CML low sokal risk on imatinib progressed to abrupt lymphoid BC-CML 15 months from diagnosis. He achieved an optimal response according European Leukemia Net criteria (2009) at 3, 6 and 12 months. No BCR/ABL point mutations were present at BC. He was treated with dasatinib 140 mg/day and he achieved morphological and molecular CR followed by aSCT from cord blood transplantation as the only option due to the lack or related or unrelated matched donor after myeloablative conditioning regimen including TBI and cyclophosphamide. The patient experienced graft failure followed by autologous reconstitution. At 2 months after aSCT due to persistence of BCR/ABL transcript the patient received ponatinib 15 mg/d. He received ponatinib for 13 months with transient molecular remission while waiting for a 2nd aSCT from a matched unrelated donor. Few months after his 2nd aSCT, he died from leukemia relapse. Mutation analysis was not granted at relapse.

At a median of 21 months 6 out of 7 patients have died from disease progression (Figure 1) and one patient died from septic shock after aSCT.

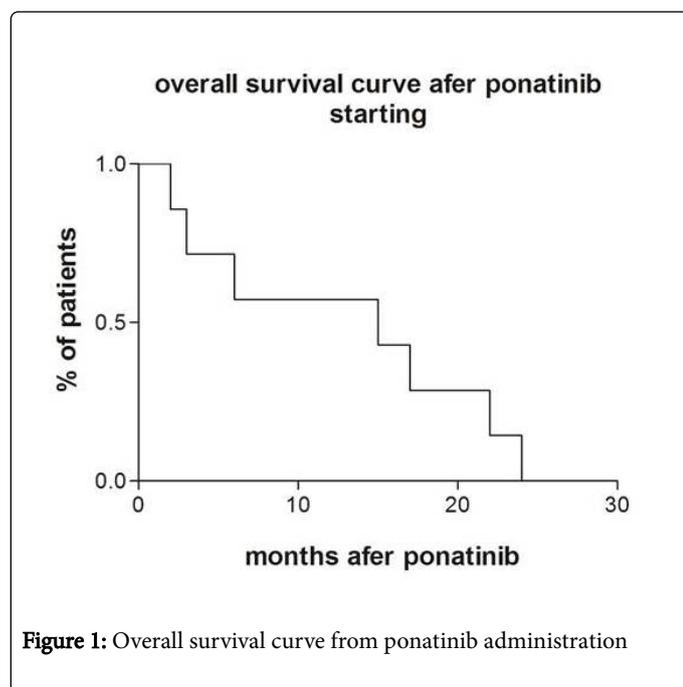


Figure 1: Overall survival curve from ponatinib administration

Discussion

Our data compares well to those reported in the PACE trial. In this study 40 patients (9% of the entire cohort) with a history of aSCT receiving ponatinib were included and results have been recently

reported at the EBMT meeting in 2015 [5]. Twenty-three percent of these patients had Ph+ ALL and 28% had BP-CML. Twelve patients had the T315I mutation detected at baseline and the majority of them had BP-CML (5 patients) or Ph+ ALL (4 patients). Twenty-five patients (63%) had an SCT \leq 2 years (but \geq 60 days) before starting ponatinib, and 15 patients (38%) had an SCT $>$ 5 years before starting ponatinib. The primary endpoint of major hematologic response by 6 months was achieved in 4/11 (36%) BPCML patients, and 1/9 (11%) Ph+ ALL patients. Major molecular response at any time was achieved in 3/11 (27%) BP-CML patients but not in Ph+ ALL patients.

Two additional cases of ponatinib successfully given for advanced leukemia relapse after aSCT were recently reported [6] One Ph+ALL patient received ponatinib and donor lymphocyte infusions (DLI) after her 2nd relapse occurring after a second aSCT and the other patient, affected by a late relapse of CML after aSCT, received both ponatinib and DLI. Mutation analysis was negative in both patients at the time of introduction of ponatinib.

In our experience ponatinib, given as bridge to transplantation or at relapse after aSCT, had little activity in patients with advanced phase Ph+ ALL or lymphoid BC-CML. Hematological response were typically seen rapidly in almost all patients and occasionally morphological and molecular response were achieved but unfortunately they were short-lived.

Resistance to ponatinib in our series of patients was accompanied to the emergence of compound mutations in 2 out of 5 patients assessed for mutations according to literature [7] or the presence of little clones with mutations not surely associated to clinically relevant drug resistance. Current data with ponatinib and chemotherapy in newly diagnosed Ph+ALL clearly advocate for its use in first line treatment [8].

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