CASE REPORT

Haematological complete remission by ponatinib and bortezomib in a patient with relapsed, Ph⁺ pre-B acute lymphoblastic leukaemia

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SUMMARY

A 74-year-old man was previously diagnosed with BCR-ABL1-positive pre-B cell acute lymphoblastic leukaemia (pre-B ALL) based on bone marrow cytology, flow cytometry, cytogenetics and fluorescent in situ hybridisation findings. Following a highly complicated hospital course, the patient achieved cytogenetic remission by consolidated chemotherapy and the tyrosine kinase inhibitor dasatinib. He subsequently presented with relapsed pre-B ALL after 3 years in remission. In consideration of his challenging clinical history, he was started on concurrent ponatinib (45 mg daily) and bortezomib (1.3 mg/m² intravenous weekly). The major molecular response was achieved (<0.0893% BCR-ABL1 transcripts) after 3 months. Bone marrow now demonstrates a BCR-ABL1-negative, complete cytogenetic response. The patient continues to do well with mild thrombocytopenia and improved anaemia on bortezomib and 30 mg daily ponatinib. Our experience with a single patient suggests the feasibility of combined targeted therapy with ponatinib and bortezomib. This novel treatment approach achieved clinical remission with a manageable toxicity profile.

BACKGROUND

Acute lymphoblastic leukaemia (ALL) with a positive Philadelphia (Ph⁺) chromosome comprises approximately 20–30% of adults diagnosed with ALL.¹ In itself, Ph⁺ ALL is considered a negative prognosticator with short remissions and poor response to standard ALL chemotherapy.^{2–4}

The Ph chromosome BCR-ABL1 translocation results in a fusion gene that encodes a constitutively active tyrosine kinase and promotes unregulated cell division. Tyrosine kinase inhibitors (TKIs) were adopted into induction protocols after several positive studies that demonstrated activity in relapsed disease.^{5–6} Studies using the first-generation TKI imatinib showed high complete remission (CR) rates compared with the pre-TKI era (95% vs 60–80%).^{7–11} However, 20–30% of patients will develop either primary or secondary imatinib resistance^{12–13} with multiple underlying resistance mechanisms. Second-generation TKIs (dasatinib, nilotinib) are active among 35–63% of imatinib-resistant patients, who may again develop resistance or become intolerant to these agents. Sequential TKI administrations may also contribute to compound mutations, that is, the occurrence of multiple mutations at the kinase-binding domain that confer a high level of resistance.^{14–15}

The third-generation TKI ponatinib has shown remarkable activity in patients with multi-TKI-resistant disease. Cortes *et al*¹⁶ recently reported that 43% of 32 patients with heavily pretreated, Ph⁺ ALL achieved a major haematological response or better (27% with a major cytogenetic response or better) with ponatinib. These patients were resistant or intolerant to dasatinib or nilotinib,¹⁶ including some with the BCR-ABL1 gatekeeper mutation T315I. The promising results of this trial call for novel, ponatinib-based approaches that can further enhance the clinical response rates in relapsed, Ph⁺ ALL.

CASE PRESENTATION

A 74-year-old man from the Middle East, with a history of coronary artery disease and type 2 diabetes, presented to the hospital in 2010 with anaemia, thrombocytopenia, and blasts in peripheral blood. Six weeks prior to admission, the patient noticed the development of scattered ecchymoses over his body. In the intervening weeks, he was progressively dyspnoeic on exertion with fatigue and generalised malaise. His white cell count on admission was approximately 35 000/μL with 83% blasts. On physical examination, he had no detectable hepatomegaly or splenomegaly. His lymph node examination was normal. A lumbar puncture was performed and was negative. Bone marrow clot and biopsy were both hypercellular (70%) and comprised more than 90% of blasts. Flow cytometric analyses revealed a clonal population of lymphocytes with the phenotype of CD20, Tdt⁺, CD34, HLADR⁺, CD19, CD10. A minor subset was CD13[–] and CD33⁺. Cytogenetics was positive for BCR-ABL1 p190 fusion transcript by fluorescent in situ hybridisation (FISH). Bone marrow clot and aspirate histopathology confirmed the diagnosis of pre-B cell ALL (pre-B ALL). The patient was initiated on induction with hyper-CVAD (course A: cyclophosphamide, vincristine, doxorubicin; course B: methotrexate, cytarabine) and imatinib. Imatinib was dosed at 100 mg/day. Imatinib was changed to the second-generation TKI dasatinib (100 mg/day) due to severe myalgias.

The patient had a complicated hospital course with a protracted ileus, debility, malnutrition, volume overload and neutropenic fever. He developed candidaemia and was admitted to the intensive care unit. A repeat bone marrow performed at 4 weeks after initiation of the therapy and following myeloid recovery showed no evidence of leukaemic involvement according to morphology.

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Molecular studies including routine cytogenetics and FISH were negative for the previously described BCR-ABL1 fusion transcript.

In view of the patient's significant toxicities from induction cytotoxic chemotherapy, he was consolidated to single agent 6-mercaptopurine and subsequently low-dose vincristine. In addition, he received several rituximab infusions. He was continued on dasatinib and standard intrathecal prophylactic chemotherapy with methotrexate. The patient had issues with hypogammaglobulinaemia which required monthly intravenous immunoglobulin infusion. Cytomegalovirus viraemia was treated with gancyclovir.

INVESTIGATIONS

In mid-2013, after approximately 3 years of remission while on dasatinib at 100 mg/day, this patient presented with worsening fatigue. Laboratory analysis revealed progressive anaemia, thrombocytopenia and 3% circulating blasts on his peripheral blood smear indicative of relapsed disease. A bone marrow biopsy confirmed relapse with 88% variable-sized lymphoblasts consistent with his prior pre-B ALL cytogenetics. BCR-ABL1 mutational analysis revealed no expression of the gatekeeper T315I mutation, but the patient was positive for the V299 L alternative splicing mutation.

TREATMENT

Given the patient's clinical history, we considered an alternative treatment to cytotoxic chemotherapy. The patient was started on concurrent standard dose ponatinib (45 mg daily) and bortezomib (1.3 mg/m² intravenous weekly). This combined treatment was well tolerated, with dramatic improvements of his severe anaemia and thrombocytopenia from relapsed disease.

OUTCOME AND FOLLOW-UP

Since initiation of second-line therapy, this patient has had resolution of blasts in the peripheral blood stream. His blood counts have improved significantly. His restaging marrow showed a haematological CR after 6 weeks of therapy, though FISH still showed positivity for BCR-ABL1. More recently, he achieved a major molecular response (MMR) after 3 months of therapy, with BCR/ABL1 transcripts at <0.0893%. Bone marrow now demonstrates a complete cytogenetic response (CCyR) with negative BCR-ABL1 gene rearrangement by FISH. The patient continues to do well with mild thrombocytopenia (platelet 96 000–120 000/mm³). Anaemia improved to an Hgb of 12 g/dL from 8.0 g/dL at pretreatment. He has been in complete haematological remission since August, 2013, and gained a CCyR with maintenance ponatinib (45 mg daily) and bortezomib (1.3 mg/m² weekly).

DISCUSSION

As a third-generation TKI, ponatinib has a potency that is >400-fold higher than imatinib¹⁷ and demonstrates remarkable activity in patients with multi-TKI resistant phenotypes that include T315I. The recently updated trial report by Cortes *et al*¹⁶ confirmed ponatinib efficacy in heavily pretreated, patients with Ph⁺ leukaemia who became resistant or intolerant to dasatinib or nilotinib. Responses were generally durable and observed regardless of baseline BCR-ABL1 kinase domain mutation status. No single BCR-ABL1 mutation has been found to be resistant to ponatinib. With a median follow-up of 15 months, 55% of 83 patients with accelerated phase chronic myelogenous leukaemia had a major haematological response and 39% had a major cytogenetic response at 12 months post-treatment. Thirty-one per cent of blast-phase CML achieved a major

haematological response and 23% had a major cytogenetic response. Among the 32 patients with Ph⁺ ALL, 43% had a major haematological response or better and 27% had a major cytogenetic response or better.

These promising findings call for novel approaches that can further enhance the clinical response to ponatinib in relapsed, Ph⁺ ALL. Previously, Dewar *et al*¹⁸ showed that the proteasome inhibitor bortezomib effectively induced durable complete haematological, cytogenetic and molecular remission in a single patient with Ph⁺ ALL. The putative mechanism of action was through blockade of FoxO3 degradation.^{18 19} FoxO3 is a member of the Forkhead family of tumour suppressors, a PI3-K/Akt effector and regulator of cellular fate through its proapoptotic features. Dewar showed that clinical remission by bortezomib was accompanied by 'rescue' of FoxO3 expression in the patient with Ph⁺ ALL refractory to standard therapies.¹⁸ This is consistent with preclinical findings of attenuated FoxO3 tumour suppressor activity by virtue of elevated proteasomal degradation in BCR-ABL1-transformed cells. These preliminary evidence suggest that bortezomib was a feasible therapeutic option in Ph⁺ ALL where FoxO3 was downregulated. Bortezomib also enhanced the antileukaemic activity of chemotherapy or targeted agents of BCR-ABL1+ leukaemia cells.^{20 21}

The clinical course of our patient is interesting for several reasons. First, despite high-risk disease and inability to tolerate full-dose consolidation, he achieved CR for approximately 3 years with a second-generation TKI. Second, he now maintains haematological remission after disease relapse, and more recently a CCyR by the third-generation TKI ponatinib combined with bortezomib. His clinical course is an example of how targeted therapies for blood malignancies continue to change disease course. It also demonstrates the prevalence of acquired resistance and how targeted therapy needs to be altered to combat resistance mechanisms. Lastly, it supports the use of bortezomib in combination with TKI-targeted therapy which has not been studied extensively.

Cortes *et al*'s¹⁶ study documented a cumulative incidence of 11.8% for serious arterial thrombotic events over 24 months of ponatinib exposure. In view of a steady increase in the number of serious vascular occlusion events during continued safety monitoring, the US Food and Drug Administration (FDA) requested, and ARIAD complied voluntarily to suspend the marketing of ponatinib on October, 2013, pending incorporation of new safety measures. The FDA subsequently approved resumption of ponatinib marketing in December 2013 following the inclusion of boxed warnings regarding arterial and venous thrombosis and occlusions that have occurred in at least 27% of patients treated with ponatinib, as well as increased incidence of heart failure and hepatotoxicity. Further, drug indication is narrowed to adult patients with T3151-positive chronic myeloid leukaemias, T3151-positive Ph⁺ ALLs or the same types of leukaemias for whom no other TKI therapy is indicated. Dosage and administration recommendations are also revised to state that the optimal dose of ponatinib has not been identified. The recommended starting dose remains at 45 mg (orally once daily) with additional disclosures regarding dose decreases and discontinuations. Commercial distribution of ponatinib has now resumed.

Our experience with a single patient shows a manageable toxicity profile in combination with bortezomib, suggesting feasibility of this approach if carefully monitored. In view of the FDA warning and recent findings that the risk of thrombotic events may be higher in patients with increasing age, our patient is seen monthly to monitor for side effects. In addition, his dose

of ponatinib has been lowered to 30 mg/day since November 2013 in the hope to avoid significant toxicity.²² Further trial-based investigation with accompanying molecular analyses will better define the clinical parameters of this combined regimen and underlying biomolecular mechanisms in Ph⁺ ALL.

Learning points

- ▶ We confirmed that durable cytogenetic remission (3 years) can be achieved by second-line dasatinib and consolidated chemotherapy for this patient with high risk, BCR-ABL1⁺ pre-B cell acute lymphoblastic leukaemia.
- ▶ For treatment of the patient's relapsed leukaemia, ponatinib in combination with bortezomib has been administered for 6 months with a manageable toxicity profile.
- ▶ This combination treatment markedly improved the patient's clinical performance including achievement of CCyR. Thus, incorporation of bortezomib with ponatinib may be applicable for optimising the therapeutic outcome in relapsed, BCR-ABL1⁺ leukaemias.

Contributors SR, YL and CM participated in the care of patient in case study. CM is the attending physician and managed the patient's care from point of initial diagnosis. YL is consultant for this patient's clinical care. YL and CM designed treatment strategy at the time of patient relapse. SR and AWT prepared the initial manuscript draft. AWT reviewed the relevant findings in patient's clinical history, prepared the Discussion Section and Learning Points based on the literature review, finalised and revised the case report. All the authors participated in the review of the final manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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