

Isolated CNS Blast Crisis of CML in A Patient on Dasatinib Therapy

Rehab Al-blooshi¹, Dimitrios Vergidis² and Jeffrey H Lipton^{3*}

¹Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, Ontario, Canada

²Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario, Canada

³Department of Medical Oncology and Hematology, Princess Margaret cancer center, Toronto, Ontario, Canada

*Corresponding author: Jeffrey Lipton, PhD, MD, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada, Tel: +1-416-946-2266; E-mail: Jeff.Lipton@uhn.ca

Rec date: May 07, 2016; Acc date: June 09, 2016; Pub date: June 13, 2016

Copyright: © 2016 Al-blooshi R, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

We report a case of a young male with chronic phase CML who despite achieving an excellent response to dasatinib therapy, developed isolated CNS blast crisis even though this tyrosine kinase inhibitor is the only one reported to cross the blood brain barrier.

Keywords: Chronic phase; Leptomeningeal disease; Hematologic remission; Hydrocortisone; Radiation oncology

Introduction

Second generation TKIs have proven efficacy as first line treatment of chronic phase chronic myeloid leukemia, with superiority in achieving CCyR and MMR over imatinib therapy, and with lower rates of progression to accelerated and blast phase when compared to imatinib [1,2]. Dasatinib is the only TKI reported to cross the blood brain barrier [3,4]. We report a case of isolated CNS blast crisis in a chronic phase CML patient who achieved CHR and MMR while on primary dasatinib therapy.

Case Report

A 32 year old male, was diagnosed with chronic phase CML on October 2014. He was found to have massive splenomegaly but no other physical findings. Laboratory showed a WBC of $140 \times 10^9/L$, Hb 68 gm/L, platelets of $97 \times 10^9/L$ with a left shift granulopoiesis. His Sokal score was 1.1 (intermediate risk). He was started on Dasatinib 100 mg daily and achieved a rapid hematologic response and three log reduction in BCR/ABL transcripts (MMR) by February 2015.

In June 2015, he started developing headaches that lasted for several hours. He had a normal brain CT scan and subsequently started to develop double vision, nausea, and ringing in his ears. He was found to have a swollen optic nerve and ophthalmoplegia. Lumbar puncture demonstrated the presence of leukemic blasts in his fluid. His immunophenotyping confirmed the diagnosis of lymphoid blast crisis CML. A brain MRI indicated diffuse leptomeningeal disease with/or perivascular disease. His bone marrow however, continued to show ongoing hematologic remission. A stable molecular response of 2.8 log reduction in BCR/ABL transcripts was confirmed in an IS standardized laboratory, on peripheral blood. There was no identified ABL1 kinase domain mutation by Sanger sequencing.

He was managed by increasing his Dasatinib dose to 140 mg once daily in addition to CNS directed therapy, no other systemic chemotherapy introduced. He had 6 lumbar punctures with triple chemotherapy consisting of Methotrexate, Cytarabine and

hydrocortisone, initially at twice weekly and then once weekly with a good response. Between the 5th And 6th lumbar punctures, the leukemic blasts had cleared. Intrathecal chemotherapy every 3-4 weeks was then continued as maintenance. His symptoms were very much improved. He received triple intrathecal chemotherapy for a total of 10 doses.

By late September however, 10 months from diagnosis, he complained of a red eye and headache. He had no cranial nerve palsy identified. Repeated lumbar puncture showed the reappearance of malignant cells. Brain MRI showed orbital infiltration. He was restarted on intensive triple intrathecal therapy and there was been slight improvement.

He was referred to radiation oncology and received a total dose of 24 Gy (12 fractions, given as 200cGy BID over 6 days) to his cranio-spinal axis, and treatment included both his orbits and eyes, because of infiltration in his orbits. He finished treatment in late October 2015. His 2 siblings were not HLA matched. An unrelated 10/10 matched donor was identified.

He underwent allogenic stem cell transplantation, using a fludarabine/busulfan 4 GyTBI conditioning regimen on January 7th 2015. His lumbar puncture was negative with undetectable BCR/ABL transcript prior to BMT. Immunosuppression was discontinued by 8 weeks as there was minimal GVHD. A planned series of 6 post transplant lumbar punctures with chemotherapy is planned. Dasatinib at 50 mg daily while he was on posaconazole and then 100 mg daily was also initiated at day 60 post bone marrow transplant with a plan for 2-3 years of therapy. Day 60 bone marrow showed complete remission and peripheral blood BCR/ABL transcripts showed no detectable disease.

Discussion

Treatment options for patients with newly diagnosed chronic phase CML have expanded over the past decade. Second generation TKI have proven efficacy as first line treatment as well as for patient intolerant and/or failed imatinib therapy.

DASISION and ENESTnd studies showed superiority of dasatinib and nilotinib in achieving CCyR and MMR over imatinib therapy, and

lower rates to progression to accelerated and blastic phase. No survival advantage has been demonstrated [1,2].

The prevalence of extramedullary blastic crisis of CML is 5-10% and specifically CNS disease is extremely rare as a site involvement [5]. Similarly CNS involvement in ph+ve ALL is 17% [6]. Our patient had a rapid hematologic response and three log reduction in BCR/ABL transcripts (MMR), surpassing ELN landmarks [7] but developed CNS blast crisis.

Isolated CNS involvement in patient with CML has been reported especially in patient on imatinib therapy [8]. Dasatinib has been reported to cross the blood brain barrier in patients with CNS disease [9-14]. We are reporting two episodes of isolated relapse of CNS blast crisis in a CML patient who had achieved prompt and durable CHR and MMR while on dasatinib therapy. It would be thought that the CNS response should be as deep as the systemic response, but this was not the case.

Developing leptomeningeal disease with cranial nerve palsies while sustaining a hematologic and molecular remission while on dasatinib, is unusual in the absence of ABL1 kinase domain mutations [15]. Cell numbers in the CSF were inadequate to determine if an isolated clone containing a dasatinib resistant mutation somehow proliferated in this sanctuary site. It is also possible that although dasatinib does enter the CSF, the effective drug concentration in the CSF is not adequate to treat established chronic phase CML in that site, and thus allowing disease progression locally. Since lumbar puncture is not a routine part of the work up of a newly diagnosed chronic phase CML patient, it is not known how common this is. This may also account for cases of isolated CNS relapse of CML post allograft.

CNS directed therapy with triple IT chemotherapy and increasing the dose of dasatinib lead to clearance of the blasts, but unfortunately in two months he relapsed again. Treatment option due to high risk disease and poor outcome [6] is to proceed with more intensive therapy, cranial-spinal radiation, allogeneic bone marrow transplant and maintenance intrathecal chemotherapy. Whether this will improve his survival is yet to be determined.

It is difficult to make a case for looking for CNS disease routinely in chronic phase CML especially at diagnosis, unless there is an initial presentation with CNS symptoms or signs such as retinal hemorrhages. This case does however; suggest that even with the broader distribution of dasatinib as compared to other TKIs, it alone is inadequate for the therapy of blast crisis CML or Ph-positive ALL if CNS involvement is present and that we should not overlook lumbar puncture and intrathecal chemotherapy if necessary, as a necessary part of the therapy of advanced disease.

References

1. Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, et al. (2014) Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 123: 494-500.
2. Giles FJ, Rosti G, Beris P, Clark RE, le Coutre P, et al. (2010) Nilotinib is superior to imatinib as first-line therapy of chronic myeloid leukemia: the ENESTnd study. *Expert Rev Hematol* 3: 665-673.
3. Takayama N, Sato N, O'Brien SG, Ikeda Y, Okamoto S, et al. (2002) Imatinib mesylate has limited activity against the central nervous system involvement of Philadelphia chromosome-positive acute lymphoblastic leukaemia due to poor penetration into cerebrospinal fluid. *Br J Haematol* 119: 106-108.
4. Porkka K, Koskenvesa P, Lundán T, Rimpiläinen J, Mustjoki S, et al. (2008) Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood* 112: 1005-1012.
5. Rajappa S, Uppin SG, Raghunadharao D, Rao IS, Surath A, et al. (2004) Isolated central nervous system blast crisis in chronic myeloid leukemia. *Hematol Oncol* 22: 179-181.
6. Lazarus HM, Richards SM, Chopra R, Litzow MR, Burnett AK, et al. (2006) Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. *Blood* 108: 465-472.
7. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, et al. (2013) European Leukemia Net recommendations for the management of chronic myeloid leukemia. *Blood* 122: 872-884.
8. Bujassoum S, Rifkind J, Lipton JH (2004) Isolated central nervous system relapse in lymphoid blast crisis chronic myeloid leukemia and acute lymphoblastic leukemia in patients on imatinib therapy. *Leuk Lymphoma* 45: 401-403.
9. Gutiérrez-Aguirre H, García-Rodríguez F, Cantú-Rodríguez O, González-Llano O, Jaime-Pérez J, et al. (2011) Effectiveness of dasatinib in relapsed CNS, Ph+ ALL that is refractory to radiochemotherapy plus imatinib: a case report. *Clin Adv Hematol Oncol* 9: 875-878.
10. Kondo T, Tasaka T, Matsumoto K, Matsumoto R, Koresawa L, et al. (2014) Philadelphia chromosome-positive acute lymphoblastic leukemia with extramedullary and meningeal relapse after allogeneic hematopoietic stem cell transplantation that was successfully treated with dasatinib. *Springerplus* 3: 177.
11. Fuchs M, Reinhöfer M, Ragoschke-Schumm A, Sayer HG, Böer K, et al. (2012) Isolated central nervous system relapse of chronic myeloid leukemia after allogeneic hematopoietic stem cell transplantation. *BMC Blood Disord* 12: 9.
12. Shoumariyeh K, Bubnoff N (2014) Long-term safety and efficacy of dasatinib in the treatment of chronic-phase chronic myeloid leukemia patients resistant or intolerant to imatinib. *Blood and Lymphatic Cancer: Targets and Therapy* 2014: 81-89.
13. Lai SW, Huang TC, Chen JH, Wu YY, Chang PY, et al. (2015) Dasatinib as the salvage therapy for chronic myeloid leukemia with blast crisis and central nervous system involvement: A case report. *Oncol Lett* 9: 1957-1961.
14. Jain A, Gupta N (2016) Isolated CNS Blast Crises in Chronic Myeloid Leukaemia Presenting as Hypertrophic Pachymeningitis and Bilateral Optic Neuritis: A Case Report. *J Clin Diagn Res* 10: OE01-OE05.
15. Gaur S, Torabi AR, Corral J (2014) Isolated central nervous system relapse in two patients with BCR-ABL-positive acute leukemia while receiving a next-generation tyrosine kinase inhibitor. *In Vivo* 28: 1149-1153.