Prolonged Survival of a Patient with Chronic Myeloid Leukemia in Accelerated Phase with Recurrent Isolated Central Nervous System Blast Crisis

Ahmed A. Bin Salman
Abdul Rehman Zia Zaidi
Syed Yasir Altaf
Nawal F. Alshehry
Imran K. Tailor
Ibraheem H. Motabi
Syed Ziauddin A. Zaidi

Corresponding Author: Ahmed A. Bin Salman, e-mail: bensalman_a@hotmail.com

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Patient: Female, 57-year-old
Final Diagnosis: CML accelerated phase with two isolated CNS blast crisis
Symptoms: Headache
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual clinical course
Background: Chronic myeloid leukemia (CML) is usually a tri-phasic myeloproliferative neoplasm, characterized by the presence of the BCR-ABL1 fusion gene, derived from a balanced translocation, t(9;22)(q34;q11). BCR-ABL tyrosine kinase inhibitors (TKI) are used to treat patients with CML. The addition of pegylated interferon-α2b to imatinib or dasatinib results in promising deep molecular responses. Because imatinib shows poor penetration into the central nervous system (CNS), the CNS may become a sanctuary site in patients on prolonged imatinib therapy for CML. It is extremely rare for the blast phase in patients with chronic phase CML to affect the CNS without concomitant bone marrow involvement.

Case Report: This report describes a 57-year-old woman who was diagnosed with accelerated phase (AP) CML and failed high dose imatinib therapy. Despite achieving an excellent molecular response to dasatinib in 6 months, she developed recurrent isolated CNS blast crisis. Survival was prolonged after treatment with intrathecal chemotherapy and whole-brain radiation therapy combined with dasatinib. After achieving long and deep molecular remission with dasatinib and a few months of pegylated interferon-α2a, she lived for 18 months in treatment-free remission (TFR). At age 65 years, she died of progressive rectal carcinoma with septic shock, cancer-related venous thromboembolism, and a possible autoimmune disorder.

Conclusions: This patient with accelerated phase CML and 2 isolated CNS blast crises died in TFR 8.5 years after her initial diagnosis and 7.5 years after her first isolated CNS blast crisis. Survival resulted from tailoring of therapies around her comorbidities.

MeSH Keywords: Blast Crisis • Central Nervous System • Chemoradiotherapy • Injections, Spinal • Leukemia, Myelogenous, Chronic, BCR-ABL Positive

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Background

Chronic myeloid leukemia (CML), a myeloproliferative neoplasm, is usually a triphasic disease, consisting of chronic, accelerated, and blastic phases. CML is characterized by the BCR-ABL1 fusion gene, which is generally derived from a balanced translocation between the long arms of chromosomes 9 and 22, (9;22)(q34;q11), resulting in a derivate chromosome known as the Philadelphia (Ph) chromosome. Globally, CML has an incidence of 1–2 patients per 100,000 adults and accounts for approximately 15% of newly diagnosed cases of leukemia in adults [1]. CML accounts for 12.5% of all leukemias in the adult population of Saudi Arabia [2].

Blast crisis in CML may be myeloid, lymphoid, or of mixed lineage. Myeloid blast crisis is twice as common as lymphoid blast crisis. Approximately 20% of patients who have CML blast crisis and are treated with imatinib experience a relapse in the central nervous system (CNS), despite a complete response in the peripheral bone and blood marrow (BM). This observation suggests that imatinib has poor penetration through the blood-brain barrier [3].

Several studies have evaluated whether tyrosine kinase inhibitors (TKIs) can be safely discontinued in patients who have achieved long-term deep molecular responses, including the Stop Imatinib (STIM) [4], TWISTER [5], STOP 2G-TKI [6], ENEST freedom [7] and EURO-SKI [8] trials, the latter being the largest trial to date on TKI discontinuation in CML patients.

The addition of pegylated interferon-α2b to imatinib or dasatinib results in promising deep molecular responses that compare favorably with those observed with either TKI alone, suggesting that these combinations may increase the likelihood of treatment-free-remission (TFR) [9,10].

This report describes the prolonged survival of a CML patient in accelerated phase (AP) who experienced recurrent isolated CNS relapses and was treated successfully. After initial diagnosis, she showed minimal response to imatinib doses as high as 600 mg/day. Treatment with dasatinib for 4.5 years resulted in an early molecular response, followed by treatment with dasatinib and pegylated interferon (Pegasys®) for 20 months (interrupted). She then remained off treatment in deep molecular remission for 18 months before dying of a rectosigmoid adenocarcinoma, septic shock, cancer-related venous thromboembolism, and possible autoimmune disorder. To our knowledge, this is the longest survival reported to date in a patient with CML-AP and double isolated CNS blast crises.

Case Report

The patient provided written informed consent for all described treatments. The Institutional Review Board (IRB) of our institution provided an exemption from approval for the purposes of publication.

A 57-year-old woman from Syria initially presented at our institution with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1. She had diabetes, for which she was being treated with metformin, and a vitamin D deficiency. She was diagnosed in April 2008 in Syria with Philadelphia positive (Ph⁺) CML in AP with hepatosplenomegaly. Ultrasonography at the referring hospital at the time of diagnosis showed that her spleen was 25 cm in diameter, and her liver was 22 cm in size. As suggested by the referral report, she was initially treated with imatinib for 2 years and went into hematological remission, but later showed clinical resistance to imatinib. Her imatinib dose was increased to 600 mg/day, but she was intolerant to this dose without any significant response. After 19 months, she presented again to the referring hospital with pallor and hepatosplenomegaly. Laboratory findings showed a hemoglobin concentration of 7 g/dL, a platelet count of 194 000/μL, a white blood cell (WBC) count of 26 000/μL with 0% basophils, 1%, eosinophils and 10% blasts.

She was referred to our tertiary care hospital with CML in AP. A BM test on March 1, 2010, showed hypercellular BM (90% cellularity) with 11% blasts, which were positive for CD45, CD34, CD33, and CD117 and negative for CD56. Her karyotype was 47,XX,+7,t(9,22)(q34,q11.2). Fluorescence in situ hybridization (FISH) analysis showed that 5% of 200 cells screened had BCR/ABL fusion signals. Hence, on March 7, 2010, she was switched to a second-line TKI, dasatinib, at a dose of 100 mg/day. After starting dasatinib, she showed minimal interruption of treatment, as well as occasionally receiving granulocyte-colony stimulating factor (GCSF) and blood product transfusions.

In June 2010, she presented with progressive shortness of breath, lung infiltrates, and abdominal pain. A computed tomography (CT) scan of her abdomen and pelvis revealed mild hepatosplenomegaly with portal venous hypertension and a small hypo-attenuated splenic lesion. There was no evidence of lymphadenopathy in the abdomen or pelvis, and her bowels were unremarkable. Within 6 months, she experienced complete cytogenetic remission with the disappearance of the Philadelphia chromosome and trisomy 7 (her karyotype was 46, XX). FISH was negative, and molecular analysis for BCR-ABL p210 did not show a detectable transcript. She was also negative for the JAK-2 V617F mutation.

She experienced 2 episodes of isolated CNS relapse, accompanied by normal BM findings. On the first occasion, in late June 2010, while she was in complete cytogenetic and molecular remission, she presented with severe headache, nausea, and a history of 2 generalized tonic-clonic seizures. A brain
MRI demonstrated abnormal signal intensity within the cortical sulci of both cerebral hemispheres, along with contrast signal enhancement and abnormal signal intensity of the subjacent cortical structures. The latter was more pronounced on the left side, highly suggestive of leptomeningeal infiltration in the context of leukemia (Figure 1). Cerebrospinal fluid (CSF) examination showed 130 WBCs/μL with 51% blasts and immature cells (Figure 2). Flow cytometry confirmed that 43% of myeloblasts were positive for CD34, CD117, and CD33; but all myeloblasts were negative for HLA-DR, CD3, and CD13. She was treated with dasatinib and 10 doses of triple intrathecal (TIT) chemotherapy, consisting of methotrexate (15 mg), cytarabine (50 mg), and hydrocortisone (50 mg). Her CSF became clear after 5 rounds of TIT chemotherapy. After 10 rounds, she refused further TIT chemotherapies. She was also not ready to undergo allogeneic stem cell transplantation (allo-SCT) because of its potential toxicities.

Eight months later, in February 2011, the patient again presented with a severe headache and was diagnosed with a second CNS relapse. Brain MRI showed interval improvement regarding the diffuse leukemic leptomeningeal infiltration and almost complete resolution of the previously observed diffuse pachymeningeal enhancement in the supra- and infratentorial locations (Figure 3). However, there was notable interval development of new, non-enhancing patchy T2 hyperintensity at the temporopolar regions bilaterally and in the frontal subcortical white matter, which was considered to be a sequela of leukemic infiltration. CSF showed a blast population (52%) expressing CD34, CD117, CD33, CD13, and CD7.

The second isolated CNS relapse was treated with whole-brain radiation therapy (30 Gy in 10 fractions). The patient was maintained on 100 mg/day dasatinib as she had shown remarkable response to it, with deep molecular remission in both peripheral blood and BM samples. However, she continued to have significant fluctuating hepatosplenomegaly, with a CT scan in March 2012 showing a spleen size of 18 cm. A repeat BM biopsy in June 2012 showed BM cellularity of 50%, characterized by trilineage hematopoiesis with <1% blasts, indicating that her relapse was controlled. Cytogenetic analysis was normal (46,XX). The combination of apparent molecular remission but ongoing hepatosplenomegaly was intriguing.

In July 2013, she was diagnosed with hypothyroidism and started on levothyroxine. Although minimal pleural effusion was ongoing, she was effectively managed with diuretics and occasional GCSF support, which was required to maintain a reasonable neutrophil count. Dasatinib was decreased to 70 mg/day because of these signs and symptoms but increased to 100 mg/day in February 2014. Dasatinib treatment was halted in September 2014 because of diarrhea and edema. Quantitative RT-PCR showed that BCR-ABL transcripts were undetectable. She was started on pegylated interferon-α2a...
(PegINF-α2a; Pegasys; Hoffman-LaRoche), at doses ranging from 45 to 135 μg. Although hepatosplenomegaly was resolved, she was unable to tolerate PegINF-α2a. Because she remained persistently negative for BCR-ABL, PegINF-α2a was discontinued in June 2016. Her spleen, however, again started to grow slowly. This was most likely an aspect of a new autoimmune disorder, as she also had joint pains, minimal left-sided pleural effusion, and chronic diarrhea. Tests in November 2016 showed that she was positive for lupus anticoagulant, antinuclear antibody (ANA), anticardiolipin IgG and IgM antibodies,
B2GP1, and anti-dsDNA antibodies. The patient refused prophylactic anticoagulation. She was referred to the rheumatology department but could not be seen due to compliance/logistic issues. Ultrasonography on 29 January 2017 showed that her spleen size had reached 17.1 cm. At this point, CML therapy had been on hold since June 2016, and she was in continuous deep molecular remission, as evidenced by undetectable BCR-ABL transcripts on 8 October 2017. During this period, she was successfully treated for 2 isolated CNS relapses while maintaining a deep systemic response.

Unfortunately, due to insurance coverage issues, her file was closed. In late August 2017, the patient developed bloody diarrhea. An endoscopic biopsy in an outside facility in September 2017 showed that she had developed an adenocarcinoma of the rectum with invasion of the uterus.

Finally, she returned to our institution with septic shock and was admitted to the intensive care unit. CT imaging of her abdomen and pelvis on 27 November 2017 (Figure 4) showed a wedge-shaped splenic infarct at the lower pole measuring 5.8×3 cm.

**Figure 4.** Composite radiological images comparing abdomen and pelvic CT scans at the time of diagnosis in June 2010 (left) and 7 years later in November 2017 when the patient was in treatment-free remission (right), showing the disappearance over time of splenomegaly.
along with interval development of moderate to massive ascites, and omental thickening with peritoneal deposits. The adnexal mass on her left side had increased in size, to 7.7×6 cm, and she had developed a new adnexal mass on her right side, measuring 6×6.7 cm. CT also showed that a diffuse long segment of the rectal mass had infiltrated into the anal canal and surrounding soft tissue, and nodules were noted. Bilateral inguinal lymph nodes showed an interval increase in size, with one reference left inguinal node measuring 2.3×2.1 cm, suggesting disease progression. A non-occlusive thrombosis of the left external iliac and visualized common femoral veins was observed. Bilateral minimal pleural effusions with basilar

Table 1. Hematological and molecular response of patient during the course of treatment.

| Course of treatment | White blood cells (×10^9/L) | Hemoglobin (g/dL) | Platelets (×10^9/L) | Bone marrow blasts (%) | Karyotype/ FISH for BCR: ABL | RTQ-PCR for BCR: ABL p210 | Overall systematic and CNS remission status |
|---------------------|-----------------------------|-------------------|--------------------|------------------------|------------------------------|--------------------------|---------------------------------------------|
| At diagnosis        | 26×10^9/L with (Eosinophils: 1% Basophils: 0% Blasts: 10%) | 7 g/dL | 194×10^9/L | 11% blasts with increased eosinophilic & basophilic precursors | 47,XX, +7, t(9,22) (q34,q11.2) FISH showing BCR-ABL fusion signals in 5% scored nuclei | 86.7% | CML – Accelerated Phase |
| At 24 months (on Imatinib) | 2.36×10^9/L | No immature cells | 9.48 g/dL | 85.4×10^9/L | 1% blasts with normal myeloid immunophenotype | 46, XX[20] FISH negative for BCR-ABL fusion signal | 0.001048 (IS) | CML in deep molecular remission |
| At 1st CNS Blast Crisis (on TIs and Dasatinib) | 4.84×10^9/L | No immature cells | 9.82 g/dL | 145×10^9/L | <1% blasts with hypocellular bone marrow with a cellularity of 30% | 46, XX[20] FISH negative for BCR-ABL fusion signal | 0.000131 (IS) | Isolated CNS Blast Crisis (CSF had 31% blasts by morphology and 43% of myeloblasts by flow cytometry) with deep molecular remission in bone marrow |
| At 2nd CNS Blast Crisis (On WBR and Dasatinib) | 1.32×10^9/L | No immature cells | 10.1 g/dL | 151×10^9/L | 1% blasts with marrow cellularity of 50% | 46, XX[20] FISH negative for BCR-ABL fusion signal | 0.00019% (IS) | Isolated CNS Blast Crisis (CSF had 50% blasts by morphology and 52% of myeloblasts co-expressing CD7 by flow cytometry) with deep molecular remission in bone marrow |
| On start of PEG-Interferon α | 1.42×10^9/L | No immature cells | 8.9 g/dL | 115×10^9/L | Patient refused bone marrow biopsy | 46, XX[20] FISH negative for BCR-ABL fusion signal | 0.0012% (IS) | In deep molecular remission, and CNS clear |
| On end of PEG-Interferon α | 1.12×10^9/L | No immature cells | 9.1 g/dL | 195×10^9/L | Patient refused bone marrow biopsy | 46, XX[20] FISH negative for BCR-ABL fusion signal | Not detected | In deep molecular remission, No CNS manifestations |
| During treatment free remission | 5.53×10^9/L | No immature cells | 9.3 g/dL | 330×10^9/L | 46, XX[20] FISH negative for BCR-ABL fusion signal | Not detected | In deep molecular remission, No CNS manifestations |

Table 1. Hematological and molecular response of patient during the course of treatment.
atelectasis and minor traction bronchiectasis in the left lower lobe basal segment were also observed. Another CT scan showed pulmonary embolism with bilateral pulmonary nodules. The patient was seen by our medical oncology team and deemed unfit for chemotherapy. She was provided with palliative supportive care.

The patient died on 28 December 2017 of septic shock, cancer-related venous thromboembolism, a possible autoimmune disorder, and progressive adenocarcinoma of the rectum for which only supportive therapy could be offered. Of note, this patient with AP CML and 2 episodes of isolated CNS relapse and died at age 65 years in treatment-free remission of 18 months, which began 8.5 years after initial diagnosis and 7.5 years after first isolated CNS relapse due to the tailoring of therapies around her comorbidities (Table 1, Figure 5).

**Discussion**

This study describes a 57-year-old woman with accelerated phase CML who failed high dose imatinib. Despite showing an excellent molecular response to dasatinib treatment for 6 months, she developed recurrent isolated CNS blast crises. Her survival was prolonged by treatment with dasatinib plus intrathecal chemotherapies at first relapse and dasatinib plus whole-brain radiation therapy at second relapse. Long and deep molecular remission was achieved by treatment with dasatinib and PegINF-α2a for a few months, followed by treatment-free remission. She died at age 65 years of septic shock, cancer-related venous thromboembolism, a possible autoimmune disorder, and progressive adenocarcinoma of the rectum for which only supportive therapies could be offered. In standard practice, TKIs are discontinued during the first chronic phase of CML after maintenance of deep molecular remission for 2–3 years. This was demonstrated feasible in our patient with CML in AP during deep molecular remission [11–13].

To our knowledge, this is the first case report of a CML patient who survived after 2 CNS blast crises and then died in complete molecular remission (CMR) while off therapy.

The TKIs commonly used to treat CML are imatinib, nilotinib, dasatinib, bosutinib, and ponatinib. Imatinib produces complete cytogenetic responses (CCRs) in about 76.2% of patients [14]. Nevertheless, it does not penetrate well into the CNS [15,16]. Several studies have assessed whether TKIs can be successfully discontinued in patients with CML who have achieved CCR and deep molecular remission lasting a few years [4–8]. Few studies to date have described patients who developed isolated CNS blast crisis during the course of CML. Dasatinib has been reported to cross the blood-brain barrier and to be effective for treating Ph+ leukemia in the CNS [17]. Dasatinib maintenance following allo-SCT has the potential to prevent CNS relapse, as shown in a patient with sustained CMR in both BM and CNS for 8 months after allogeneic HSCT [18]. Other studies have suggested, however, that dasatinib may fail to prevent CNS relapse [19,20].

An effective approach to increase the potential for treatment-free remission (TFR) may be the addition of PegINF-α2a to imatinib or dasatinib, as combination treatment results in deep molecular responses, comparable to those observed with TKIs alone [9,10]. Intrathecal chemotherapies have also been shown effective in treating CNS blast crises [21].

A report of a patient with an isolated CNS blast crisis and review of 23 other patients found that 5 of these patients developed an isolated CNS relapse at a median 3.1 years after allo-SCT [22]. In addition, a 64-year-old woman with blast crises CML who was treated with unrelated allo-SCT developed an isolated CNS relapse 18 months later, which was treated with triple intrathecal chemotherapy and dasatinib. She survived for 3 years but later died of advanced vulva carcinoma [23]. One patient diagnosed with chronic phase CML in October 2014 and treated with 100 mg/day dasatinib experienced 2 CNS relapses, the first...
in June 2015, which was successfully treated with 140 mg/day dasatinib plus intrathecal chemotherapy while BM was in chronic phase; and the second in September 2015, which was treated with 24 Gy radiation followed by unrelated 10/10 matched donor allo-SCT [24]. Another study described a patient with chronic phase CML who initially presented with extramedullary CNS and lymph node blast crises that were treated with dasatinib 70 mg orally twice daily and a standard AML induction regimen along with 16 doses of intrathecal methotrexate/cytarabine/hydrocortisone and 24 Gy of radiation [25]. Because of the patient’s poor general condition, allo-SCT was not advisable. The patient remained in complete cytogenetic and molecular remission, on single-agent dasatinib for 4 years with no evidence of active extramedullary disease according to his most recent brain MRI performed 4 months prior to the writing of this report [25]. Splenomegaly persisted for some time in our patient, despite her being in CMR, and disappeared following treatment with PegINF-α2a, which acts as an immunotherapeutic agent.

Conclusions

In conclusion, we report the longest survival to date of a patient who experienced 2 episodes of isolated CNS blast crises during her course of CML in AP. She was treated successfully with individually tailored therapy, surviving for 116 months after the diagnosis of CML in AP. She died in treatment-free remission of 18 months, 90 months after her first isolated CNS relapse, without employing allo-SCT. Discontinuation of TKI is currently recommended as standard practice in the first chronic phase of CML. The feasibility of this approach was demonstrated in our patient while she was in deep molecular remission.

Isolated CNS relapses can occur in patients with BCR-ABL-positive CML while receiving imatinib or a next-generation TKI. Achievement of complete cytogenetic and molecular responses in BM may not be sufficient to prevent CNS relapse. Clinical vigilance is required to detect isolated CNS blast crisis in CML patients, even if they are in deep molecular remission. Patients with vague CNS symptoms should undergo CSF analysis and brain MRI. Aggressive intrathecal chemotherapy and craniospinal irradiation can effectively control CNS disease and significantly prevent mortality. Concurrent continuation of an appropriate TKI with better CNS penetration and/or pegylated interferon, as well as consideration of allo-SCT, are potential therapeutic modalities in preventing relapse and possible achievement of cure.

We are in the process of systematically analyzing the demographic characteristics of similar patients and therapeutic strategies used in their treatment, to provide further insight into the management of isolated blast crises during CML.

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Conflict of interests

None.

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