Published in final edited form as:
Leuk Res. 2008 September ; 32(9): 1468–1471. doi:10.1016/j.leukres.2008.02.001.

Secondary Myelodysplastic Syndrome in a Patient with Philadelphia-Positive Acute Lymphoblastic Leukemia after Achieving a Major Molecular Response with HyperCVAD plus Imatinib Mesylate

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Abstract

The addition of imatinib to high-intensity chemotherapy has improved the outcome of patients with Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL). However, the possible long-term side effects of this combination are not yet known. Development of new clonal abnormalities in complete cytogenetic remission after treatment with imatinib has been reported in patients with chronic myeloid leukemia but not in patients with Ph-positive ALL. Here, we present a patient with Ph-positive ALL who received hyperCVAD plus imatinib and achieved hematologic, cytogenetic, and major molecular responses. The patient then developed myelodysplastic syndrome and solitary central nervous system relapse of ALL.

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Conflict of interest and contributions
Arturo Vega-Ruiz - Nothing to declare
Wrote the manuscript
Susan O'Brien – Nothing to declare
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Jorge Cortes – In receipt of research funding from Novartis Pharmaceuticals
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Partow Kebriaei – Nothing to declare
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Deborah Thomas – Nothing to declare
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Hagop Kantarjian - In receipt of research funding from Novartis Pharmaceuticals
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Keywords

Philadelphia-positive acute lymphoblastic leukemia; imatinib mesylate; myelodysplastic syndrome

1. Introduction

Most adult patients with Philadelphia (Ph) positive acute lymphoblastic leukemia (ALL) have a dismal prognosis. About 80%–85% of patients with Ph-positive ALL achieve a complete hematologic response (CHR), depending on the treatment regimen; however, the disease-free survival rate at 2 years is estimated to be only 10%–15% in patients who are treated with only chemotherapy [1]. Adding imatinib mesylate, a specific inhibitor of the BCR-ABL oncoprotein, to standard chemotherapy regimens has improved the event-free survival [2–4], but the long-term side effects of imatinib mesylate therapy, if any, are still unknown.

Several studies have reported the development of new clonal abnormalities in Ph-negative metaphases after treatment with imatinib in patients with chronic myeloid leukemia (CML) [5–11]. A number of these patients have dysplastic features in their bone marrow, and a few patients developed acute myeloid leukemia (AML)[5,7,12–14]. However, the relationship between the development of cytogenetic abnormalities, myelodysplastic syndrome (MDS), or acute leukemia and treatment with imatinib is not clear. Many patients treated with imatinib develop cytopenias and dysplastic changes in their bone marrow. However, in most cases, these abnormalities are transient. [15,16] Whether imatinib induces MDS remains to be established.

Here, we report a patient with Ph-positive ALL who received hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone (hyperCVAD) plus imatinib. After 11 months of therapy, the patient developed MDS. Her clinical course was further complicated by the development of a CNS relapse shortly after, though the patient remained in complete hematologic, cytogenetic, and major molecular remission.

2. Case Report

A 62-year-old woman presented in March 2006 to her local practitioner with recurrent sinus infections, bone pain, and fatigue. Evaluation of the patient's blood count revealed a white blood cell count of 22×10^9/l, with 82% blasts. A physical examination did not show any remarkable findings. Bone marrow examination was consistent with a diagnosis of pre–B-cell ALL (immunophenotype positive for CD9, CD10, CD13 dim, CD19, CD22, CD25, CD34, CD38, CD79a, and TdT). A chromosome analysis revealed the presence of the Ph chromosome and trisomy 8. Molecular studies detected the b3a2 BCR-ABL fusion transcript, and the BCR-ABL/ABL transcript ratio was 53.5(Table 1). The initial lumbar puncture (LP) revealed CNS infiltration.

In May 2006, the patient began induction therapy with hyperCVAD plus oral imatinib mesylate 600 mg/day, which was given throughout the course of treatment. After the first treatment cycle, the patient achieved a CHR, and the transcript ratio decreased to 0.14. The

immunophenotype analysis indicated that in spite of CHR, minimal residual disease (MRD) was still present. The patient's cerebrospinal fluid (CSF) became negative after the third round of intrathecal chemotherapy. A subsequent LP found no CNS infiltration. Subsequently, LPs were performed and intrathecal chemotherapy was administered weekly for 6 more weeks.

Following the fifth course of treatment, the patient remained in CHR, and a bone marrow biopsy showed complete cytogenetic remission, negative fluorescence in situ hybridization (FISH), negative flow cytometry for MRD, and a BCR-ABL/ABL transcript ratio of 0.003. Due to the patient's poor performance status and multiple co-morbidities, intensive chemotherapy was stopped in September 2007. The patient then began receiving maintenance therapy with prednisone, vincristine, and imatinib 800 mg/day.

In November 2006, 3 months after starting maintenance therapy, cytogenetic analysis of bone marrow revealed a pseudodiploid clone, inv(6)(p21.1p22) in two metaphases and del(20)(q11.2p13.3) in one metaphase. These abnormal metaphases suggested an emergent population of neoplastic cells, although there was no dysplasia and no increase in blasts. Flow cytometry and FISH were negative for MRD, and the BCR-ABL/ABL transcript ratio was 0.08. Clinically, the patient remained stable, and continued the maintenance regimen.

In March 2007, the dose of imatinib was reduced to 600 mg/day due to the development of fluid retention. The patient also developed cytopenias without the need for growth factor therapy or transfusions. In April 2007, a repeat bone marrow exam showed no blasts but 34% monocytes and occasional promonocytes, with dyserythropoiesis which suggested therapy-related MDS. She also developed peripheral blood monocytosis, up to 3.7×10^9/L, that could not be attributed to any other ongoing process. On karyotype analysis, a pseudodiploid clone t(4;11)(q21;q23) was identified, and FISH was positive for a clone with an *MLL* gene rearrangement. The inv(6) and del(20) clones present in the previous cytogenetic test were not seen. It was then concluded that the monocytosis and clonal cytogenetic abnormalities represented therapy-related MDS. This case was classified as chronic myelomonocytic leukemia type 1 by French-American-British criteria. Flow cytometry results remained negative for MRD. The BCR-ABL/ABL transcript ratio was less than 0.01.

In August 2007, the patient underwent a stem cell transplant evaluation. The patient was asymptomatic, with a marked improvement in her performance status, and remained in major molecular remission. The work-up prior to stem cell transplant revealed CNS infiltration by leukemic cells, and immunophenotype analysis revealed these cells to be lymphoblasts; CSF was positive for BCR-ABL by polymerase chain reaction. After further intrathecal chemotherapy, the BCR-ABL fusion disappeared from the CSF. She then underwent a matched sibling allogeneic stem cell transplant. At the latest follow-up, she had no evidence of active leukemia in her bone marrow, and no CNS or extramedullary disease. She had full donor hematopoiesis without cytogenetic abnormalities.

3. Discussion

In this case report, our patient with Ph-positive ALL achieved hematological remission after the first course of chemotherapy with imatinib. After 5 courses of treatment, she also achieved cytogenetic and molecular remission. While receiving maintenance with imatinib, vincristine and prednisone, she developed new clonal abnormalities and morphological findings associated to MDS. Several cytotoxic agents have been associated with the development of MDS with specific chromosomal abnormalities. Alkylating agents are mostly associated with losses or deletions in chromosome 7 and/or 5, while drugs targeting DNA-topoisomerase II (e.g., etoposide, doxorubicin, daunorubicin, mitoxantrone) have been associated with balanced translocations involving chromosome bands 11q23 and 21q22 [17]. Methotrexate and 6-mercaptopurine have been reported to interact with DNA repair, leading to point mutations and nonhomologous recombination [18]. Development of MDS has been reported in patients with CML receiving imatinib who achieve complete hematologic, cytogenetic, and molecular responses [12–14]. Chromosomal abnormalities in Ph-negative metaphases after imatinib therapy have been reported in 2%–17% of patients with CML [5]. The most frequent cytogenetic abnormalities are trisomy 8, monosomy 5 or 7, and 20q- and changes in chromosome Y [5–7].

Our patient developed clonal abnormalities 7 months after the initiation of chemotherapy and while receiving maintenance therapy. The abnormalities initially were nonspecific, but we eventually detected a clone with the translocation (4;11) and *MLL* gene rearrangement, findings clearly associated with MDS and acute leukemia. Around 5%–10% of *MLL* gene associated leukemias (i.e., myeloid or lymphoid leukemia) are therapy related [19–21]. We could not determine which drug was responsible for the development of the new chromosomal abnormality in our patient. It is also possible that a silent clone present at the onset, emerged after the Ph clone was partially eliminated. Other reports of secondary AML or MDS occurring after ALL therapy exist in the literature [17]; however, to our knowledge, no cases of secondary MDS have been reported after hyperCVAD plus imatinib therapy.

Our patient also developed a solitary CNS relapse, which was confirmed to be ALL by immunophenotype analysis and polymerase chain reaction for BCR-ABL. At diagnosis, 5%–10% of patients with ALL have evidence of central nervous system (CNS) disease. Without CNS prophylaxis, up to 30% of patients will develop CNS leukemia, and despite adequate CNS prophylaxis, up to 10% of patients will eventually develop a CNS relapse [22]. Anecdotal reports of CNS relapse in patients with Ph+ ALL despite achievement of complete hematologic, cytogenetic and molecular responses in the bone marrow have been published recently [22–26]. This may be due to the inability of imatinib to cross the blood-brain barrier and achieve adequate therapeutic concentrations in the cerebrospinal fluid [22–26]. Therefore, although solitary CNS relapse is uncommon after adequate prophylaxis, it is imperative to suspect it in patients with appropriate symptoms even in remission. Development of new tyrosine kinase inhibitors that cross the blood-brain barrier may further decrease the incidence of CNS relapse in Ph-positive leukemias.

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Table 1

Development of secondary MDS in a patient with Ph-positive ALL who had achieved complete remission.

	At diagnosis (April 2006)	After first cycle of treatment (June 2006)	After fifth cycle of treatment (September 2006)	After maintenance therapy (November 2006)	Development of MDS (April 2007)
Bone marrow biopsy	ALL L2 (FAB)	Blasts 3%	Blasts 1%	Blasts 1%	Blasts 0, monocytes 34%
Flow cytometry	pre–B-cell ALL	MRD (+)	MRD (−)	MRD (−)	MRD (−)
Cytogenetic analysis	Ph chromosome, trisomy 8	Not performed	Normal karyotype, CCR	Clone inv(6)	Clone t(4;11)
BCR-ABL/ABL transcript ratio	53.5	0.14	0.003	0.08	0.01
FISH	Not performed	Not performed	BCR/ABL (−)	BCR/ABL (−)	MLL gene (11q23) (+)
CNS infiltration	Yes	No	No	No	No