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Case Reports in Clinical Medicine

Philadelphie chromosome—Positive *de novo* acute myeloid leukemia. Isolated meningeal relapse in a patient treated with imatinib mesylate

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ABSTRACT

Acute myeloid leukemia philadelphie positive (Ph+ AML) is a rare aggressive acute leukemia with poor prognosis. We report a patient with ph positive AML (FAB5), the transcript bcr/abl was not performed at diagnosis. She achieved complete remission after conventional induction chemotherapy. The consolidation therapy was based on Imatinib only due to infectious complications. She was in complete hematologic and cytogenetic remission for 19 months, and after she exhibited an isolated meningeal relapse. A second remission was achieved with intrathecal chemotherapy and cranial irradiation. Imatinib was switched to second generation Tyrosine kinase Inhibitor which had better diffusion into cerebrospinal fluid. She is in complete hematologic, cytogenetic and meningeal remission after 14 months of treatment. Imatinib monotherapy affords insufficient protection from CNS relapse. Second generation Tyrosine kinase Inhibitor seems to have better efficiency. Ph+ AML with monoblastic differentiation should be considered, like Ph+ ALL, at high risk of meningeal leukemia and should receive central nervous system prophylaxis.

Keywords: Acute Myeloid Leukemia; Philadelphie Chromosome; Meningeal Relapse

1. INTRODUCTION

Acute myeloid leukemia philadelphie positive (Ph+ AML) is a rare aggressive acute leukemia with a poor prognosis [1]. Imatinib mesylate a selective BCR-ABL tyrosine kinase inhibitor, has shown significant antileukemic activity in patients with chronic myeloid leukemia in blastic crisis (CML-BC), acute lymphoblastic leukemia philadelphie positive (Ph+ ALL) and few reported cases of *de novo* acute myeloid leukemia philadelphie positive (Ph+ AML) [2,3]. However, a high rate of meningeal relapse was reported in imatinib-treated patients with either lymphoid or bilineage CML-BC or Ph+ ALL [4,5], no data is available about Ph+ AML. This elevated risk of meningeal relapse is probably explicated by the poor penetration of Imatinib into the cerebrospinal fluid (CSF) [4-6].

We report a patient with *de novo* Ph+ AML who has received Imatinib as consolidation therapy and presents an isolate Meningeal Relapse.

2. CASE REPORT

A 54 years old women without prior medical history, was admitted for fever and productive cough. She had a splenomegaly of 3 cm below costal margin, mandibular abce and gingival hypertrophy without lymphoadenopathy. The blood count showed hyperleucocytosis: 112.3 G/L with 70% of blasts, 7% of monocytes and 1% of myelocytes, without basophils, hemoglobin: 5, 5 g/dl, and platelet count was 132 G/l. Bone morrow aspirate reveled 86% of monoblasts. Immunophenotyping showed myeloid blasts with expression of CD13, CD33, CD117, CD34, CD15, HLADR and intracytoplasmic MPO, lymphoid markers were negative otherwise, so it was AML type M5 (FAB classification). The transcript bcr-

abl was not performed at diagnosis. The patient was treated with chemotherapy: Cytarabine 200 mg/m^2/d1 through 7 and Idarubicine 12 mg/m^2/d1 through 3. The result of karyotype analysis was available on day 10 of induction course, showed the presence of the translocation t(9,22) (q34,q11) in all analyzed metaphases, associated with chromosome seven structure abnormalities: 46 XX, t(9,22) (q34,q11) [3]/46 XX, t(9,22) (q34,q11), add 7 (p22) [3]/46 XX, t(9,22) (q34,q11), add (7) (q36) [9].

Imatinib at a dose of 800 mg/d was started at day 47 of the induction course (drug not immediately available). The patient achieved complete hematologic and cytogenetic remission after one course of chemotherapy, the transcript bcr-abl after induction was not detected on peripheral blood and bone morrow. Due to serious infection complications (pulmonary aspergillosis and Geotrichum capitatum septicemia), chemotherapy was discontinued and consolidation therapy was continued by Imatinib alone.

After 19 months of complete hematological and cytogenetic remission, the patient presented an isolated meningeal relapse. She consults for neurological signs and symptoms included severe headache, vomiting and diplopia due to a sixth nerve palsy. A cranial computed tomography, a brain and spinal magnetic resonance imaging showed no abnormalities.

The analysis of cerebrospinal fluid identifying leukemic blasts (blast count in the CSF is 900/mm^3). Hemogram, myelogram and karyotype were normal. She received central nervous system directed treatment consisting of repeated intrathecal triple agent chemotherapy (cytarabine, hydrocortisone, and metothrexate) and cranial irradiation (24 Gray) successes to achieve a second remission. The transcript bcr-abl was done after 3 intrathecal chemotherapy and was undetectable.

After the end of cranial irradiation, Nilotinib was prescribed at a dose of 400 mg twice a day.

At present, she is in complete hematologic, cytogenetic and meningeal remission after 14 months of treatment.

3. DISCUSSION

Informations concerning the efficacy of Imatinib to the Ph+ AML patients are limited to only a few cases reports. Imatinib as monotherapy failed to show efficacy as induction therapy in a case report patient [7].

Soupir *et al.* [1] reported that among seven patients with Ph+ AML who were treated with Imatinib (2 alone and 5 with conventional chemotherapy), six patients had a hematologic response although the duration was short (median, 2.5 months; range, 1 - 6 months), and one of them had a complete hematological response. In others cases reports, when Imatinib is started after obtaining CR with standard chemotherapy, it allowed to achieve or to maintain a complete cytogenetic remission and/or a complete molecular response [2,3,8].

Our patient has been in complete hematologic and cytogenetic remission for 19 months with only Imatinib maintenance at the dose of 800 mg/d. The doses reported in the literature are 400 mg and 600 mg/d. These results suggested that IM might have a positive role in consolidation and/or maintenance therapy in remission Ph+ AML patients. Although, the undetectable transcript after induction therapy is not synonym of complete molecular remission, it may not be detectable by the available technique used [9]. After 19 months of complete hematologic and cytogenetic responses, our patient exhibited an isolated meningeal relapse. The available data concerning meningeal relapse are limited to Ph+ ALL and Ph+ biphenotypic leukemia.

A high incidence of meningeal leukemia was reported in patients with a lymphoid or bilineage phenotype who didn't received CNS prophylaxis [4,5], suggesting poor penetration of Imatinib into the CSF. In these studies the concentration of Imatinib in cerebrospinal fluid (CSF) and blood was measured simultaneously. The concentration of Imatinib in CSF was lower than that in blood [4-6, 10]. The limited distribution of Imatinib to the brain has been attributed to p-glycoprotein-mediated efflux in mice [11].

Our patient had risk factors for development of central nervous system (CNS) leukemia including a high initial WBC count and FAB type (M5), but she didn't receive an adequate CNS prophylaxis. The simultaneous administration of Imatinib and cytotoxic agents including prophylactic CNS-directed therapy was not permitted because of the lack of safety data. Patel *et al.* reported subdural hematomas in three patients with Ph+ ALL receiving Imatinib mesylate in conjunction with systemic and intrathecal chemotherapy [12]. The optimal type CNS-directed treatment is not well definite; our patient had received repeated intrathecal triple agent chemotherapy in five times, allowing to sterilize the cerebrospinal fluid, and were followed by a cranial irradiation of 24 Gray and two lumbar puncture with intrathecal chemotherapy. Imatinib was replaced by Nilotinib. After 14 months the patient was still in complete cytogenetic and molecular remission.

Pfeifer *et al.* reported a prolonged complete molecular remission of 11 and 14 months after diagnosis of isolated CNS relapse in two of three patients with ALL Ph+, who presented an isolate meningeal relapse [5].

4. CONCLUSION

The Ph-translocation is a rare molecular abnormality in AML patients usually implying a poor prognosis. Treatment with Imatinib may improve the outcome, but

patients are at considerable risk of meningeal leukemia during monotherapy. They should routinely receive CNS prophylaxis, the most effective types of prophylaxis: cranial irradiation or intrathecal chemotherapy, remain to be elucidated.

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