CASE REPORT

A Case of Chronic Lymphocytic Leukaemia Occurring During Treatment of Chronic Myeloid Leukaemia

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Introduction

Chronic myeloid leukaemia (CML) and chronic lymphocytic leukaemia (CLL) are the most common types of leukaemia in elderly. The characteristic of CML is Philadelphia chromosome, because of translocation of chromosome 9 and 22 and fusion of bcr-abl gene. Result of fusion bcr-abl gene is activation tyrosin-kinase and uncontrolled proliferation of myeloid cells [1]. CLL characteristics are low proliferative activity and accumulation of monoclonal B lymphocytes in bone marrow, lymph nodes and other organs which are resistant to apoptosis. Simultaneous occurrence of CML and CLL is extremely rare. We report here a case of patient in whom CLL developed during the treatment of CML with imatinib mesilate.

Case Report

In a 64 years old woman during the routine laboratory control was found leukocytosis and thrombocytosis in peripheral blood. She didn't have any subjective symptoms or clinical findings during the first visit to doctor. There is no hepatosplenomegaly or lymphadenomegaly in physical examination. Hematological findings showed leukocytosis with granulocytes predomination and thrombocytosis in blood smear (WBC $28.9 \times 10^9/l$ and PLT $800 \times 10^9/l$), without anemia. White cell differential showed 64 %

segmented neutrophils, 4 % band cells, 20 % lymphocytes, 6 % monocytes, 2 % eosinophils, 1 % basophils, 1 % metamyelocytes, 1 % myeloblasts and 1 % promyelocytes. Bone marrow aspiration was hypercellular, with myeloid hyperplasia. Cytogenetics showed a variant Philadelphia chromosome 46,XX, t (9;11;22) (q33; p13; q11) in 27 metaphases. Radiological examination confirmed normal physical examination. Our patient was diagnosed CML in chronic phase with prognostic scores: Sokal-intermediate risk, Hasford-low risk and Eutos-low risk. Six months after diagnosis, she started with therapy of imatinib (Gleevec®) in dose of 400 mg per day. Four weeks after initiation of imatinib, she achieved complete hematological response. In that time also started adverse events of use of imatinib-muscle cramps and conjunctivitis, grade 1. Six months after, patient had mild leukocytosis, with normal value of hemoglobin and count of platelets in blood. Bone marrow aspiration and cytogenetics were repeated. Bone marrow aspiration showed decreasing ratio between granulocytic and erythroid lineage and benign lymphoid infiltrates. Cytogenetic findings was normal karyotype in 15 metaphases (complete cytogenetics response), and molecular test showed 1.17 % transcript of bcr-abl gene. After 12 months, in hematological findings there were gradual increase of leucocytes, with lymphocyte predomination and normal value of hemoglobin, count of platelets and biochemical tests. Cytogenetics test was normal and molecular test showed a major molecular response. Patient had progressive leukocytosis with lymphocytosis (WBC $42.86 \times 10^9/l$, Lymph 91 %) so reactive leukocytosis was excluded. After 16 months, hematological revision was done. Revision included cytological, cytogenetic, pathohistological analysis of bone marrow aspiration and flow cytometry analysis of peripheral blood. In physical examination there is no lymphadenomegaly or

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hepatosplenomegaly and chest X-ray and computerized tomography of the abdomen confirm that. In smear of peripheral blood was described 91 % lymphocytes, 17/100 Gumprecht's shadows/leucocytes and in bone marrow aspiration about 90 % small typical lymphocytes. Pathohistological findings in bone marrow were nodular/interstitial infiltration by cells of CLL/small lymphocyte lymphoma. A flow cytometer analysis of the patient's peripheral blood revealed a monoclonal B cell population with CD5+ and CD23+ coexpression. Cytogenetic and molecular analysis confirms maintenance of complete cytogenetic and molecular response of CML. The diagnosis of CLL in Binet A stage and Rai 0 stage was made 24 months after diagnosis CML in chronic phase. Patient was continued with therapy by imatinib mesilate, because CLL in Binet A stage didn't require any therapy. On the last hematological control, 48 months after diagnosis of CML, the leukocytosis in blood is maintained, without anemia and normal count of platelets. The values of CBC during course of CML are demonstrated in Table 1.

Discussion

Our patient represents rare case CLL during the course of treatment CML with imatinib mesilate. To literature data, only 21 patients were diagnosed with CLL prior to CML or both simultaneously, and only in 6 patients were diagnosed prior CML to CLL [1–7]. Patients with diagnosis of CLL have predisposition for occurrence secondary malignancies because of impaired immune system or hemiotherapy [8]. Secondary malignancies after CLL have usually non-hematological origin and disappear a few years after diagnosis and treatment of CLL [9]. Compared to CLL, secondary malignancies are rare after CML [10, 11]. CLL was occurred during the treatment of chronic phase of CML in five cases and during the accelerating phase of

CML in one case [1, 3–7]. In all cases, CLL was appeared after 6–74 months after diagnosis of CML and patients were between 45 and 88 years old [7]. Case of our patient correlates with existing files.

Our patient was diagnosed by CLL during the treatment imatinib mesilate, so we asked ourselves if the secondary malignancy is consequence of using inhibitor tyrosin kinase (TKI). Research of 1445 patients with CML and chronic myeloproliferative disorders on therapy by TKI during medial monitoring of 107 months, showed that 66 patients (4.7 %) were developed secondary malignancies and CLL was taken 3 %. This research didn't prove that TKI are increasing risk of appearance secondary malignancies [12]. CML and CLL have two independent clone proliferations. Crescenzi et al., in their case CLL during course of CML, was confirmed this claim. Immunophenotypisation, FISH technic and molecular analysis approved that population of clonal B cells, CD5 and CD19 positive, have IgH rearrangement and deletion 13q, without bcr-abl fusion, and the other population of cells have translocation of 9 and 22 and p210 and p190 bcr-abl himeric transcript [13].

Simultaneously treatment of CLL and CML is challenge and there is no recommendations for it. Imatinib mesilate and other TKI are initially synthesized for treatment CML [14]. Increasing activity of c-abl kinase and sensitivity CLL cells on TKI in vitro were explained using of TKI in CLL in some patients [15]. Second generation of TKI, dasatinib, has the similar effect like imatinib mesilate in treatment of CML. They inhibit pan-Src kinases and suppress leucemogenesis [2]. Kinases from Src family, including Lyn kinases, are exprimed in high concentrations in patients with CLL and have important role in proliferation and surviving malignant cells [16]. Phase 2 study of single-agent dasatinib in patients with relapsed and refractory CLL demonstrated 9 among 15 patients (60 %) had shrinkage of lymph nodes or extranodal masses to less than

Table 1 The values of CBC during course of CML

Complete blood count (CBC)	At diagnosis	Before starting imatinib	After 1 month on imatinib	After 6 months on imatinib	After 12 months on imatinib	After 18 months on imatinib	After 24 months on imatinib	After 48 months on imatinib
WBC ($\times 10^9/l$)	28.9	31.2	10.0	20.1	21.2	42.86	65.2	96.07
Hgb (g/l)	136	132	116	124	119	122	121	120
Hct	0.39	0.38	0.35	0.38	0.36	0.38	0.37	0.36
PLT ($\times 10^9/l$)	800	736	141	314	270	314	245	256
Neutrophils (%)	71	57.5	33	22.4	9.5	8	7.7	4.2
Lymphocytes (%)	20	39	59	71.9	84.9	91	86.6	83.65
Monocytes (%)	6	1.1	4	3.7	4.5	0	4.4	0.4
Basophils (%)	1	1	0	0.3	0.4	0	0.6	2.6
Eosinophils (%)	2	1.4	4	1.7	0.7	1	0.7	0.4

50 % of their original size, and 4 patients had reduction of absolute lymphocyte count by >50 %. Dasatinib clearly has activity in relapsed CLL/SLL, but responses on treatment depended of prognostic markers [17].

There is no clear attitude or guidelines for treatment patients with CML and CLL. Our patient with previously diagnosed CML, achieved complete hematological, cytogenetics and molecular remission on treatment by imatinib mesilate, so there is no reason for changing therapy. In this moment, our patient doesn't have subjective symptoms or positive physical examination, with adequate radiological and biochemical findings, so there is no activity of CLL. For now, our patient was followed and controlled every 3 months without therapy for CLL.

Increasing leukocytes count in CML patients in optimal response should remained us for an other hematological malignance-CLL. Our patient has increasing leukocyte count but in bone marrow aspiration we described benign lymphoid infiltrates which can appear in treatment with TKI, so we didn't suspect for secondary malignance [18].

TKI, especially dasatinib, has evidence based role in therapy of CML and potential role in therapy of CLL and should be adequate therapy for patients with CML and CLL [14].

Compliance with Ethical Standards

Conflict of interest Marina Dokic is member of Serbian Medical Association. Ivana Urošević has received a speaker honorarium from Novartis. She is member of American Society of Hematology, European Hematology Association and Serbian Medical Association. Ivanka Savić has received a speaker honorarium from Roche, Pfizer, MSD and Jansen. She is member of Serbian Lymphoma Group, Serbian Myeloma Group and Serbian Medical Association. Borivoj Sekulić is a member of Serbian Medical Association. Aleksandar Savić is a member of American Society of Hematology, European Hematology Association and Serbian Medical Association. Ivana Milosević is a member of European Hematology Association and Serbian Medical Association. Nebojsa Rajić has received a speaker honorarium from Novonordisk and Pfizer. He is member of Serbian Medical Association.

Ethical Approval We declare that all procedures performed in this article involving human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Written consent was obtained from the patient for publication of this case report.

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