Dasatinib-Induced Tumor Lysis Syndrome and Following Hematologic Remission in Fibrotic Blastic Crisis of CML

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ABSTRACT

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disease almost always caused by a genetic defect known as the Philadelphia (*Ph*$^+$) chromosome. Ph$^+$ chromosome is associated with a *BCR/ABL* fusion gene expressed as an oncoprotein, which is generally considered as the initiator for the chronic phase of CML. Tyrosine kinase inhibitors (TKI) are target-specific therapeutic agents that achieves successful complete responses rates for majority of CML patients. However, blastic crisis BC of CML is still a great therapeutic challenge even in the TKI era. Dasatinib is the most effective TKI for blastic phase CML, but tumor burden is very high for terminal stage of advanced CML disease. In this report, tumor lysis syndrome (TLS) with acute renal failure occurring after the dasatinib treatment initiation in BC-CML was presented. Dasatinib is effective in BC of CML and tumor lysis syndrome due to TKI effect should be taken into account during initial treatment of patients with high tumor load.

Keywords: Tumor lysis syndrome, Dasatinib, CML, Apoptosis, Acute renal failure

ÖZET

KML-Fibrotik Blastik Krizde Dasatinib'e Bağlı Tümör Lizis Sendromu ve İzleyen Hematolojik Remisyon

Kronik myeloid lösemi (KML) hemen daima Philadelphia (Ph$^+$) kromozomu olarak bilinen bir genetik defekt ile oluşturulan kronik bir myeloproliferatif hastalıktır. *Ph*$^+$ kromozomu bir onkoprotein eksprese eden *BCR/ABL* füzyon geni ile ilişkilidir ve bunun kronik faz KML'nin başlatıcısı olduğu düşünülür. Tirozin kinaz inhibitörleri (TKI) hedefe yönelik terapötik ajanlardır ve KML'li hastaların önemli kısmında tam yanıt sağlarlar. KML blastik krizi (BK), TKI varlığına rağmen tedavisi güç bir durumdur. Dasatinib blastik faz KML'de en etkili TKI'dir. Ancak ileri KML'nin bu son aşamasında tümör yükü çok fazladır. Bu vakada BK-KML için uygulanan dasatinib tedavisi sonrası gelişen tumor lizis sendromu ve akut böbrek yetmezliği sunuldu. Dasatinib KML blastik krizinde etkilidir ve yüksek tumor yüküne sahip hastalarda ilk uygulama sırasında TKI etkisine bağlı gelişebilecek tumor lizis sendromu akılda bulundurulmalıdır.

Anahtar Kelimeler: Tümör lizis sendromu, Dasatinib, KML, Apoptozis, Akut renal yetmezlik

INTRODUCTION

CML is a disorder of uncontrolled myeloproliferation of hematopoietic stem cell. It is the first cancer type that was shown to be caused by a specific chromosomal rearrangement. *Ph*+ chromosome is the result of a reciprocal translocation between chromosome 9 that contains the Abelson (ABL) kinase domain and breakpoint cluster region (BCR) on chromosome 22. This chromosomal abnormality results in the gene product *BCR/ABL*, which is a constitutively active oncogenic tyrosine kinase (TK).[1] Increased TK activity further activates intracellular pathways that lead to increased cellular proliferation, resistance to apoptosis and genetic instability.[2] Therefore, terminal blastic crisis (BC) of CML represents a great therapeutic challenge and is associated with increased mortality.

Imatinib is the first developed tyrosine kinase inhibitor (TKI) active against ABL, and competitively inhibits adenosine triphosphate binding to the constitutively active BCR/ABL tyrosine kinase therefore impedes the growth and proliferation of the malignant cells with allowing normal hematopoiesis. Imatinib has replaced stem cell transplantation as first line treatment for newly diagnosed chronic phase CML patients, but imatinib resistance is can important clinical problem. Dasatinib, is a novel second generation TKI as an effective treatment alternative for imatinib resistant or intolerant CML patients in all phases. It is a dual inhibitor of *BCR/ABL* and SRC family kinases.[3] Reported side effects of dasatinib are neutropenia, thrombocytopenia, leukopenia, anemia, diarrhea, fatigue, headache, dyspnea, rash, asthenia, nausea, peripheral edema, pleural effusion, elevated aspartate aminotransferase, elevated alanine aminotransferase, and elevated bilirubin levels.[4] We present the first documented case of TLS in a CML patient treated with dasatinib. However, this adverse effect of dasatinib is clearly associated with its efficacy in the BC of CML. Accordingly, tumor lysis due to TKI effect shall be considered during the initial treatment of blastic phase CML patients.

CASE REPORT

A 50-years old male patient diagnosed as CML six years ago and imatinib 1 x 400 mg therapy was started. After two months, imatinib treatment stopped and patient follow-up lost for 4 years until applying with blurred vision to the clinic. WBC level was 194 x 10^3/μl and in molecular analysis 22% p210 fusion transcription was detected. Imatinib treatment restarted and after one year therapy patient was complaining from malaise and fatigue. In physical examination the patient's liver was 4 cm and spleen was 2 cm below the costal margin. Laboratory values were: WBC: 29.9 x 10^3/μl, platelets: 405 x10^3/μl. Peripheral blood smear revealed 63% neutrophil, 4% basophil, 1% promyelocyte, 2% myelocyte, 4% metamyelocyte. In bone marrow analysis a hypercellular bone marrow with diffuse fibrosis and increased blasts was detected and diagnosed as blastic crisis of CML. In molecular analysis 8.7% fusion transcription was present. Since hematologic and molecular remission could not be obtained, treatment was altered to dasatinib. Allopurinol (300 mg/day) and dasatinib (100 mg/day) was started. The patient was admitted to emergency department 24 hours after the initiation of treatment due to complaints of fever, nausea, vomiting, blurred speech and distortion in consciousness. The lab values were; serum potassium: 6.12 mg/dl, creatinine: 5.8 mg/dl, blood urea nitrogen: 108 mg/dl, uric acid: 38 mg/dl, inorganic phosphate: 13.2 mg/dl, calcium: 3.6 mg/dl. The patient had uremic encephalopathy at the time of admission. Dasatinib treatment was stopped. Due to impaired renal function, allopurinol treatment was also not reinitiated. Since he had uremic symptoms and electrolyte imbalance, hemodialysis therapy was applied. After 2 sessions of hemodialysis uremic encephalopathy was relieved. Polyuria appeared on the 3th day with a urine output of 4 L/day. The patient was hydrated taking into consideration of insensible losses as well as urine output. On the 8th day of follow-up, the creatinine level decreased to 1.7 mg/dL, and allopurinol therapy was initiated at a dose of 300 mg/day. On the 16th day of follow-up, the renal function was completely improved. In later follow-ups WBC count was decreased to 1.5 x 10^3/μl. Bone marrow analysis at this period was found hypercellular. Dasatinib treatment was restarted at a dose of 1 x 50 mg. Renal functions were not affected during the course. The patient was discharged with dasatinib treatment. In outpatient controls WBC was in normal range and hematologic remission achieved. At the end of the 2nd month of treatment

the patient was applied to emergency department with high fever, cough and septic symptoms. The patient died from pneumonia and sepsis during the hematological remission stage of BC-CML.

DISCUSSION

TLS describes systemic metabolic imbalances due to rapid tumor cell death especially following the initiation of cytotoxic therapy. This syndrome is most common in patients with lymphoproliferative malignancies although it can be seen in patients with solid tumors. Due to rapid destruction of tumor cells and extracellular displacement of a great amount of intracellular content, hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and uremia can occur. These metabolic disturbances can lead to acute renal failure and can be fatal. Aggressive hydration and diuresis, control of hyperuricemia with allopurinol prophylaxis, and vigilant monitoring of electrolyte abnormalities are the backbone in prophylaxis and treatment.[5] Chronic phase CML is considered as low risk for TSL development. Acute myeloid leukemia with WBC levels between 25 and 100 x 10^3/μl is considered as medium risk and when WBC level is more than 100 x 10^3/μl considered as high risk.[6] The patient reported here had received dasatinib treatment 24 hours before his admission to the hospital, did not have a very high blood cell count, but had hepatomegaly and splenomegaly. The patient's disease status of fibrotic blastic phase CML represented the risk for TLS development. In myeloproliferative diseases such as CML, TLS may develop due to insensible tumor load due to organomegaly and despite low peripheral WBC count, TLS risk should still be considered and suitable prophylactic measures must be taken.

This is the first reported case of TLS with acute renal failure due to dasatinib administration. Dasatinib is a dual inhibitor of bcr/abl and Src kinases.[3] Src kinases represent a family of nonreceptor intracellular tyrosine kinases that regulate signal transduction pathways involved in cell growth, differentiation, and survival.[7] Binding of dasatinib to these kinases inhibits their autophosphorylation and downstream phosphorylation of additional targets and thus blocks the oncogenic activities.[1]

TLS is seen most often following chemotherapy induction of tumor cells, due to massive cell death and lysis of cell contents.[8] However, TKIs are believed to induce TLS via apoptosis.[9] Expression of bcr/abl in cell lines prevents apoptosis[10] and down-regulation of bcr/abl enhances the rate of spontaneous or drug induced apoptosis in CML cell lines and clinical samples.[11] Dasatinib has shown to inhibit cell proliferation and apoptosis induction by Stat5 blockage.[12]

However, apoptosis produces little or no inflammation, since cell remnants are absorbed by especially macrophages, rather than being discharged into the extracellular space. But the non-cleared apoptotic cells become secondarily necrotic and release their intracellular contents into the surrounding tissue, consequently prompt cytotoxic and inflammatory reactions. Therefore, the appropriate removal of apoptotic cells is mandatory for protection of tissues from harmful exposure to the potentially cytotoxic and inflammatory intracellular contents of dying cells.[13] We speculate that in this current case TLS developed because dasatinib caused massive apoptotic cells by removing apoptosis blockage bcr/abl tyrosine kinase inhibition and ineffective removal of these cells have led to secondary necrosis, causing TLS.

Dasatinib is the most effective TKI in the blastic phase of CML. However the tumor burden is very high in those terminally handicapped subpopulation of CML. Even the initial peripheral WBC count is low, those patients with BC-CML must be closely monitored by clinical and laboratory follow-up. Vigorous hydration and administration of allopurinol are recommended during both TKI regimen and chemotherapy.

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