Imatinib-Induced Tumor Lysis Syndrome: Report of a Case and Review of the Literature

Hung Chang, MD; Lee-Yung Shih, MD

Imatinib is a selective tyrosine kinase inhibitor which acts on breakpoint cluster region-Abelson fusion gene (BCR-ABL) positive leukemia including all phases of chronic myeloid leukemia and acute lymphoblastic leukemia. It may induce rapid apoptosis and subsequent tumor lysis syndrome. Only 3 cases of imatinib-induced tumor lysis syndrome have been reported. We herein described an additional patient with BCR-ABL (e1a2) positive acute lymphoblastic leukemia who developed tumor lysis syndrome after 10-day treatment with imatinib. Experience in the current case suggests that preventive measures for tumor lysis syndrome, including allopurinol and hydration, should be taken for patients with high leukemia burden who receive imatinib therapy, and parameters of tumor lysis should be monitored in the early phase of therapy. *(Chang Gung Med J 2008;31:510-4)*

Key words: imatinib, tumor lysis syndrome, chronic myeloid leukemia, acute lymphoblastic leukemia

Philadelphia chromosome (Ph), t(9;22)(q34;q11) is the hallmark in the diagnosis of chronic myeloid leukemia (CML), which results from the fusion of the Abelson (ABL) proto-oncogene on chromosome 9 to the breakpoint cluster region (BCR) gene on chromosome 22. The BCR-ABL fusion gene encodes BCR-ABL chimeric protein with constitutive tyrosine kinase activity.[1] The Philadelphia chromosome can be found in up to 20-40% of adult acute lymphoblastic leukemia (ALL) and less than 5% of acute myeloid leukemia (AML).[2] Imatinib is a selective inhibitor of the BCR-ABL oncoprotein. It has been used in the treatment of CML and Philadelphia chromosome positive ALL and AML with variable responses.[1-3] Tumor lysis syndrome is a constellation of elevated uric acid, phosphate, potassium and lactate dehydrogenase (LDH) levels, hypocalcemia and renal failure induced by rapid apoptosis of cells.[4] It may develop spontaneously before therapy or occur after antineoplastic therapy in patients with a high leukemia burden. Imatinib treatment may cause tumor lysis syndrome but the true incidence is obscure; in a review of the English literature, only 3 cases have been described.[5-7] We report another case and review the clinical picture, risk factors, management and prophylaxis for imatinib-induced tumor lysis syndrome.

CASE REPORT

In August, 2003, a 30 year-old man presented with spontaneous gum bleeding and body weight loss of 6 kg over 2 months. A nasopharyngeal tumor was found and a biopsy was done at the same time. The pathology report showed it was a lymphoblastic lymphoma. He was admitted to the hematology ward. On admission, the physical examination revealed pale conjunctiva and multiple enlarged

From the Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan
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Correspondence to: Dr. Hung Chang, Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital. No. 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.) Tel.: 886-3-3281200 ext. 2524; Fax: 886-3-3286697; E-mail: horng@cgmh.org.tw

lymph nodes 1 to 2.5 cm in the cervical and axillary areas. The spleen was palpable 9 cm below the left costal margin. The liver was not palpable. The hemogram showed extreme leukocytosis (white blood cell 383,000/μL, blasts 74.3%). A routine biochemical profile revealed uric acid 16.4 mg/dL, LDH 172 U/L, aspartate aminotransferase (AST) 19 U/L, alanine aminotransferase (ALT) 10 U/L, bilirubin 0.5 mg/dL, blood urea nitrogen (BUN) 27 mg/dL, creatinine 1.4 mg/dL, calcium 9.1 mg/dL, phosphate 4.3 mg/dL and potassium 5.3 mg/dL. Bone marrow aspiration cytology revealed he had precursor B cell acute lymphblastic leukemia (ALL, L1) with lymphoblasts accounting for 93% of all nucleated cells. Flow cytometry showed the leukemic cells were positive for CD19, CD10, CD22, and CD34 and negative for CD5, CD7, CD33, CD13, CD41, CD117, CD56, and surface and cytoplasmic immunoglobulin. Cyto-genetic analysis showed a result of 46, XY but reverse transcriptase polymerase chain reaction (RT-PCR) for BCR-ABL fusion transcript was positive (e1a2). The patient was given rasburicase 0.2 mg/kg per day for 6 days. The follow-up biochemistry data showed uric acid was less than 0.1 mg/dL, creatinine 0.9 mg/dL, calcium 8.8 mg/dL, phosphate 4.8 mg/dL, LDH 69 U/L and potassium 4.8 mg/dL.

Chemotherapy was initiated with ALL-Berlin-Frankfurt-Munster (BFM) 86 proctocol,[8] which included prednisolone 60 mg per day, followed by weekly doxorubicin 45 mg/m^2 and vincristine 2 mg for 4 cycles and intermittent asparaginase 5,000 IU/m^2. He had no remission after treatment for one month. We changed the treatment to cytarabine 1,000 mg/m^2 every 12 hours for 4 days and etoposide 200 mg per day for 3 days. Pneumonia and respiratory failure developed during the myelosuppression period. He was intubated and treated for pneumocystis carinii pneumonia although a bronchioalveolar lavage had a negative result on Giemsa stain. He was weaned from the ventilator. The result of bone marrow examination in November still showed no remission with blasts accounting for 70.1% of all nucleated cells. Because of poor physical performance following respiratory failure, antineoplastic treatment was not given for 6 weeks, after which he started to take imatinib 400 mg per day. Just before we initiated imatinib, his hemogram was hemoglobin 10 g/dL, platelets 189,000/μL, white blood cells 77,900/μL, blasts 62%, neutrophils 2.3%, monocytes 1.0%, and lymphocytes 34.8%. The spleen was palpable 1 cm below the left costal margin. Ten days after commencing treatment, he had a rapid decline in cell count (hemoglobin 5.8 g/dL, platelets 139,000/μL and white cells 1,300/μL, neutrophils 63%, monocytes 3%, lymphocytes 34%). The spleen was impalpable. The bone marrow examination revealed cellularity 10-30% with blasts accounting for 1.4% of all nucleated cells. RT-PCR of a bone marrow specimen still showed a positive result for BCR-ABL fusion transcript (e1a2). Biochemistry data showed uric acid 23.5 mg/dL, BUN 69 mg/dL,creatinine 4.9 mg/dL, calcium 7.0 mg/dL, phosphate 8.1 mg/dL LDH 34 U/L and potassium 4.6 mg/dL. He was given allopourinol, hydration and urine alkalization. The follow-up data on day 3 of this treatment showed uric acid 9.2 mg/dL, BUN 19 mg/dL, creatinine 1.8 mg/dL, calcium 6.0 mg/dL, phosphate 2.8 mg/dL LDH 57 U/L and potassium 3.1 mg/dL. On day 6, uric acid was 5.7 mg/dL, creatinine 1.4 mg/dL, calcium 7.4 mg/dL, phosphate 2.5 mg/dL LDH 57 U/L and potassium 3.0 mg/dL. Imatinib was withdrawn on day 3 and resumed at a dose of 200 mg per day on day 6. He had a nearly normal hemogram in one month (hemoglobin 12 g/dL, platelets 258,000/μL and white cells 8,100/μL, neutrophils 58.5%, monocytes 14.5%, lymphocytes 25.5%, eosinophils 0.5% and basophils 1%). However, he discontinued imatinib at the end of February for economic reasons. In April 15, he had an overt relapse (white blood cells 26,100/μL, blasts 46.3%). He was lost to follow up and sought alternative treatment at home.

DISCUSSION

Imatinib has demonstrated significant activity in all phases of CML and Ph(+) ALL.[1,3,5] In an early study, the treatment of CML with imatinib induced a response of more than 90% and a cytogenetic response of more than 50%.[1] For BCR-ABL positive ALL, Ottman et al. observed a complete hematologic response of 29% in a total of 56 patients.[3] However, this was transient, with only 6% of patients sustaining a response over 4 months with a median time to progression of 2.2 months.

As in chemotherapy, treatment with imatinib may cause tumor lysis syndrome. We found only 3 such cases in the literature, one of which was briefly mentioned in a dose escalation pilot study,[5] one in a

patient with CML[7] and another in a patient with ALL.[6] Our present patient also had ALL. The onset of tumor lysis syndrome ranged from 5 to 10 days. Dann et al. reported a patient with ALL who was treated with imatinib for only 2 days and developed tumor lysis syndrome 5 days later.[6] This illustrates the short duration needed for imatinib to induce tumor lysis syndrome.

Tumor lysis syndrome is more common among patients with high white blood cell (WBC) counts. Other features potentially associated with leukemia burdens include the spleen size, bone marrow cellularity and blast numbers. The features of the reported cases are summarized in the Table 1. In the 2 ALL cases,[6] the WBC counts were 41,000/μL and 77,900/μL. After tumor lysis developed, the WBC number declined rapidly to 700 and 1,300/μL, respectively. The spleen size was not available in the first case and was 1 cm below the costal margin in the present case. Bone marrow cellularity and blast numbers were markedly decreased in our patient but not available in the first one. In the patient with CML,[7] the WBC was 114,000/μL before and 77,600/μL after treatment. Pretreatment, the spleen was 15 cm below costal margin. Although these features suggest imatinib-induced tumor lysis syndrome is associated high leukemia burdens, it is premature to draw a conclusion from such limited data.

According to Talpaz et al., imatinib at a dose of 600 mg per day can induce a hematologic response and remission within a shorter period than a dose of 400 mg.[9] This difference in time to response may potentially affect the incidence of tumor lysis syndrome, although further solid evidence is limited by the small number of cases. In all 3 cases with available data, 400 mg or 600 mg was prescribed.[6,7] Further reports and investigation are needed to evaluate the relationship between dose and tumor lysis syndrome. In all 3 cases with available data,[6,7] imatinib was continued or only briefly withdrawn during treatment of tumor lysis syndrome. Tumor lysis syndrome resolved without recurrence in all cases. Reduced leukemia burden after initial therapy, as well as further preventive measures including hydration and allopurinol, are the keystones of safety for continuation of imatinib treatment.

The management of imatinib-induced tumor lysis syndrome is not different from that caused by chemotherapy. In the existing cases, 2 patients received hemodialysis and tumor lysis syndrome improved in 7 and 9 days.[6,7] Our patient is the only one who did not require hemodialysis. Allopurinol, hydration and urine alkalization successfully improved his condition and his creatinine normalized in 5 days. Recently, rasburicase has been used in the prophylaxis or treatment of chemotherapy-induced tumor lysis syndrome.[4] It may reduce uric acid levels within 4 hours. Our patient had received rasburicase during chemotherapy with a good effect. When tumor lysis syndrome developed after imatinib, it was managed by hydration and allopurinol. Experience with rasburicase in the treatment of imatinib-induced tumor lysis syndrome is lacking. Further study, including drug interactions, is needed to confirm its effects and advantages over conventional treatment.

Based on limited experience, some supportive measures are advised during imatinib treatment. Close monitoring of biochemical profiles is recommended in all available reports.[5-7] Allopurinol and hydration as prophylaxis are also suggested.[5,7] In view of the rapid development of tumor lysis syndrome,[6] monitoring in the early phase, especially in cases with high leukemia burden, is required. Earlier

Table 1. Clinical Features of Imatinib-Induced Tumor Lysis Syndrome Cases

Case	Diagnosis	Onset of TLS	Imatinib dose	WBC before TLS	WBC during TLS	Uric acid	Cr	Dialysis	Cr return to normal	Imatinib dose	Reference
1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5
2	ALL	5 days	600 mg	41,000	700	26	3.88	Yes	9 days	Reduced	6
3	CML	5 days	400 mg	114,000	77,600	38.4	12.7	Yes	7 days	Same	7
4	ALL	10 days	400 mg	77,900	1,300	23.5	4.9	No	5 days	Reduced	Our case

Abbreviations: TLS: tumor lysis syndrome; Cr: (serum) creatinine; NA: not available; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; WBC: white blood cells.

monitoring of the biochemistry profile is the keystone to early detection of and intervention for this side effect.

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基利克所引發的腫瘤溶解症候群之個案報告

張 鴻 施麗雲

帶有 BCR-ABL 基因的白血病，包含各時期的慢性骨髓性白血病及一部分急性淋巴性白血病。基利克是一個選擇性的酪胺酸水解酶抑制劑，可針對 BCR-ABL 基因作用而治療上述疾病。由於此作用足以引起細胞的快速凋亡，它也可能造成腫瘤溶解症候群。我們查證文獻，僅發現三例較完整之個案報告。在本文中我們報告另一例 BCR-ABL (e1a2) 陽性的急性淋巴性白血病在接受十天的基利克治療後發生腫瘤溶解症候群，本例的經驗顯示，對接受基利克治療的病患，須在早期就密切監控關於腫瘤溶解症候群的指標，對於白血病細胞負荷量大的病患應考慮給予大量水分及 allopurinol 等預防措施。(長庚醫誌 2008;31:510-4)

關鍵詞：基利克，腫瘤溶解症候群，慢性骨髓性白血病，急性淋巴性白血病

長庚紀念醫院 台北院區 血液腫瘤科；長庚大學 醫學院
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通訊作者：張鴻醫師，長庚紀念醫院 血液腫瘤科。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉2524; Fax: (03)3286697; E-mail: horng@cgmh.org.tw