Laboratory tumor lysis syndrome complicating LBH589 therapy in a patient with acute myeloid leukaemia

LBH589 is a novel cinnamic hydroxamic acid analog (HAA) pan-histone deacetylase inhibitor (HDACi) currently in early phase clinical development.

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Preliminary data about LBH589 suggests significant biological activity (both *in vitro* and *in vivo*) in solid tumor cell lines[1] and more recently, in a range of malignant hematological disorders including acute myeloid leukemia (AML).[2,3] To-date, laboratory tumor lysis syndrome[4] (LTLS) has not been described as a complication of LBH589 therapy.

We report a case of a 60 year-old man who developed LTLS following treatment for AML with oral LBH589. The patient was diagnosed with refractory anemia with excess blasts (RAEB) in July 2005. Cytogenetic analysis demonstrated trisomy 8 and del(20q). He was initially treated with standard dose cytarabine and idarubicin (7+3).[5] Post-induction bone marrow examination revealed ongoing dysplasia but no excess of myeloblasts. He subsequently received further cytarabine and idarubicin as consolidation. This was complicated by prolonged pancytopenia and subsequently by rapid progression to overt AML. Salvage therapy with FLAG[6] failed and the patient was referred to our institution for investigational therapy with LBH589.

The patient was enrolled in a Phase IA/II trial of oral LBH589 for patients with advanced hematological malignancies and commenced intermittent oral LBH589 (30 mg orally three times per week on alternate weeks [one cycle = 28 days]). The patient presented on day 14 of cycle 1 with hyperleukocytosis (WBC 68×10^9/L) and acute renal failure: creatinine 280 µmol/L (baseline 120 µmol/L). He was administered LBH589 according to protocol and was also commenced on hydroxyurea 1g b.d., allopurinol and hyper-hydration. Within 24 hours, associated with a fall in his WBC to 9×10^9/L, he developed LTLS - corrected calcium 1.91 mmol/L (2.23-2.50),

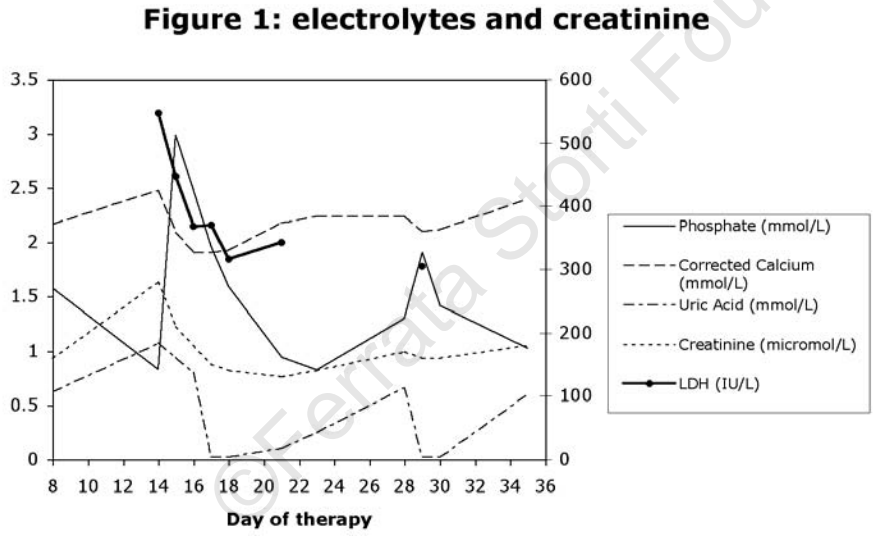

Figure 1. Response of electrolytes (phosphate, corrected calcium, uric acid and LDH) and creatinine to treatment with LBH589. LBH589 30mg administered days 14, 16, 18 and days 28, 30, 32.

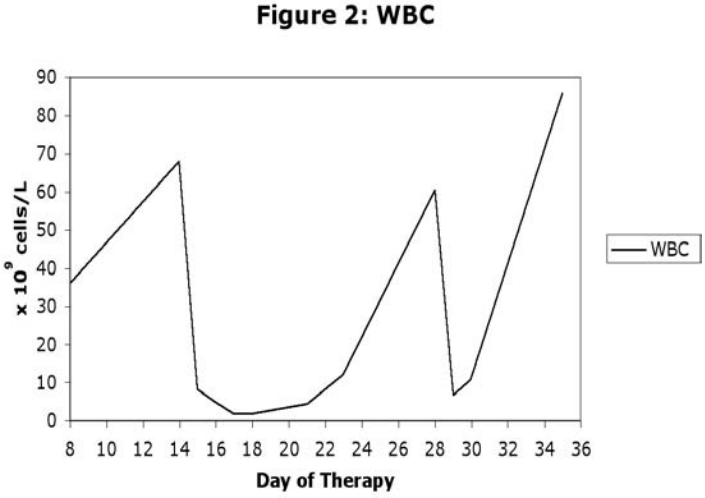

Figure 2. Response of white cell count (WBC) to treatment with LBH589. LBH589 30mg administered days 14, 16, 18 and days 28, 30, 32.

phosphate 2.99 mmol/L (0.70-1.30) and uric acid 0.8 mmol/L (0.15-0.50) (Figure 1 and 2). He recovered uneventfully following the administration of single dose of 13.5mg of rasburicase, intravenous fluid and electrolytes. Treatment with hydroxyurea was ceased and he continued LBH589 as per schedule. On day 28 (day 1 of cycle 2) with a WBC of $60x10^9$/L, LTLS again recurred within 24 hours of LBH589 administration despite prophylactic rasburicase therapy (single dose of 12 mg) and hyper-hydration - WBC fell to 6×10^9/L, corrected calcium 2.1 mmol/L, phosphate 1.91 mmol/L and uric acid <0.02 mmol/L (from 0.66mmol/L) (Figure 1 and 2). Notably, the patient was not on hydroxyurea therapy at this time, unlike the first episode of LTLS. The patient again recovered uneventfully but was taken off trial following completion of 1.5 cycles due to disease progression. He died not long after due to complications of his disease.

This first reported case of laboratory tumor lysis syndrome with LBH589 therapy clearly demonstrates the potent anti-leukemia potential of LBH589 and mandates that caution be taken with LBH589 treatment of AML patients, particularly those exhibiting highly proliferative and/or high tumor burden disease.

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