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Tumor Lysis Syndrome (TLS) Following Fludarabine Therapy for Chronic Lymphocytic Leukemia (CLL): Case Report and Review of the Literature

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Adenosine deaminase inhibitors have proven superior to alkylating agent-based therapies in inducing clinical and hematologic remissions in treated and previously untreated chronic lymphocytic leukemia (CLL) patients, and they have become increasingly accepted as a standard for therapy. We report the case of a 66-year-old patient with a 7-year history of CLL who had been previously treated with alkylating agents. Upon presentation with abdominal lymphadenopathy, a 5-day course of the nucleoside analogue, fludarabine, was administered. Two days after completion, the patient developed acute tumor lysis syndrome (TLS) that induced renal failure with hyperkalemia and hyperuricemia. This resulted in critical, life-threatening complications requiring hospitalization, aggressive hemodialysis and fluid replacement therapy. While only 5 other cases of TLS associated with fludarabine therapy have been reported since 1989, we recommend that adenosine deaminase inhibitor therapy be initiated with the addition of allopurinol, and that hydration with copious amounts of oral fluids during therapy be encouraged in order to help protect against the renal effects of potential TLS induced by these agents. Am. J. Hematol. 72:212–215, 2003.

Key words: tumor lysis syndrome; chronic lymphocytic leukemia; fludarabine; adenosine deaminase inhibitors; acute renal failure; hemodialysis

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia seen in the western world and continues to be a chronic illness of the elderly. Several new medications introduced in the past 10 years have resulted in improved ability to induce remission rates in both previously treated and newly diagnosed patients. However, none of these newer treatment modalities thus far have been shown to improve or prolong survival. Frequently this disease remains indolent for years, and therapeutic intervention for CLL is indicated when patients who have active disease become symptomatic with palpable or bulky tumors, i.e., peripheral adenopathy and/or splenomegaly, anemia, and thrombocytopenia secondary to marrow infiltration by the proliferating leukemic clone, or when an autoimmune hemolytic anemia/thrombocytopenia supervenes.

Prior to this past decade, standard treatment regimens consisted of alkylating agents with or without corticosteroids [1]. Low-dose or intermittent high-dose chlorambucil in combination with prednisone or other cytotoxic agents has served as the standard first-line treatment approach of advanced stage or symptomatic CLL. Over the past decade a new class of agents, adenosine deaminase inhibitors, was introduced that has proven superior to alkylating agent-based regimens in inducing clinical and hematologic remissions in both treated and previously untreated patients [2–8]. These agents inhibit both DNA and RNA synthesis by inhibiting DNA and RNA polymerase and ribonucleotide reductase resulting in decreased levels of intracellular deoxynucleotide [9,10]. Fludarabine, the most frequently used agent of the nucleoside analogues, is a water soluble purine analogue antimetabolite that is resistant to adenosine deaminase

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TABLE I. Blood Chemistries Indicating Tumor Lysis Syndrome After Completion of a 5-Day Course of Fludarabine Therapy and After Subsequent Hemodialysis and IV Fluid Supplementation

Lab features	48 hr post-completion of fludarabine therapy	28 hr post-hemodialysis and IV fluid therapy	16 days post-admission	14 days post-discharge
Serum potassium (mEq/L)	8.5	4.6	4.4	4.3
BUN (%)	147			
Serum creatinine (mg%)	6.9	2.1	3.1	1.8
Serum calcium (mg%)	6.5			
Ionized calcium (mg%)	3.6			
Serum phosphorus (mg%)	24.7	7.2		
Uric acid (mg%)	37.6	8.6		

and is capable of rapidly lowering the peripheral blood lymphocyte count and inducing a reversible state of lymphopenia and immunosuppression. Large clinical studies using this class of agents have shown significant depletion of both CD4 helper and CD8 suppressor T cells, resulting in an increased incidence of life-threatening systemic infections [11,12]. Other complications or adverse effects caused by this family of nucleoside analogues include pancytopenia, neurotoxicity, and the precipitation of autoimmune hemolytic anemia. Other agents used in a wide variety of combinations as salvage regimens, some in conjunction with monoclonal antibodies, are also being tried in an effort to induce durable and prolonged remissions [13]. Again, none of these agents used alone or in combination have been able to improve survival in treating CLL, thus far.

Tumor lysis syndrome (TLS) is a rare complication of the treatment of CLL and has seldom been a concern with any of he chemotherapeutic regimens that have been traditionally and currently used, including the nucleoside analogues. In our search of the English literature, we were able to find only five cases of TLS associated with fludarabine therapy since 1989 and a review of this complication has estimated an incidence of 0.33% with supporting clinical and laboratory features [14–19]. We have recently seen one case of TLS in a patient who was classified as Rai stage III disease after the administration of the first cycle of fludarabine and had previously received alkylating agent therapy.

CASE REPORT

A 66-year-old white male with a history of CLL who had been previously treated with alkylating agents in 1994 and 1996 was initially seen in consultation in September 2001 when he began to have vague, abdominal pain, and discomfort associated with weight loss and anorexia. At that time a CT scan of the chest, abdomen, and pelvis showed a large left pleural effusion, hepatosplenomegaly, and extensive abdominal lymphadenopathy. A thoracentesis was performed and showed a monoclonal population of lymphoid cells positive for CD20 and CD19 on flow cytometry, consistent with CLL. At that time his white blood cell count was 62,500, with 94% lymphocytes and a normal hemoglobin and platelet count. Because of the persistent abdominal pain, discomfort and evidence of abdominal and retroperitoneal adenopathy, a decision was made to treat him with fludarabine 25 mg/m^2 daily for 5 days.

Although his symptoms improved after the first three days of therapy, his oral intake and urine output decreased during the fifth day of the chemotherapy. Forty-eight hours after completion of the 5-day course of fludarabine, the patient was admitted to the hospital from the emergency room where he presented with weakness, lethargy, and dehydration. He was hyperkalemic and azotemic with a serum potassium of 8.5 mEq/L, BUN 147 mg%, serum creatinine 6.9 mg%, serum calcium 6.5 mg% with an ionized calcium of 3.6 mg%. Serum phosphorus was 24.7 mg%, and a uric acid was 37.6 mg% (Table I). An EKG showed peaked T waves, absent P waves, and a prolonged PR interval. A chest X-ray showed a large left pleural effusion. His O_2 saturation on room air was 88%. The patient was promptly started on intravenous fluids with glucose, insulin, and calcium chloride added to the intravenous fluids.

Hemodialysis was started shortly after his transfer to the intensive care unit. A diagnosis of TLS with metabolic acidosis (pH 7.32) was made and the patient's clinical and laboratory status improved with the intravenous fluid therapy and dialysis. Twenty-eight hours after his admission his serum potassium was down to 4.6 mEq/L, serum creatinine dropped to 2.1 mg%, and his phosphorus was 7.2 mg%. His uric acid fell to 8.6 mg%. The patient was discharged from the hospital 16 days after his admission with a serum creatinine of 3.1 mg% and a potassium of 4.4 mEq/L. When he returned to the outpatient clinic 2 weeks subsequent to his discharge from the hospital, his serum creatinine was 1.8 mg% and his potassium was 4.3 mEq/L. He refused any additional chemotherapy and died 1 month later from causes unrelated to the CLL or TLS.

DISCUSSION

TLS is a unique complication of treatment of a variety of malignant diseases that results from cytoreductive

therapy. It is most often associated with chemotherapy and occurs most frequently with cytotoxic agents used in the treatment of hematologic malignancies. The highest risk of this complication is associated with aggressive cytoreductive therapy commonly used in patients with leukemias and malignant lymphomas in which a high percentage of the tumor cells are rapidly proliferating and are exquisitely sensitive to the chemotherapy [20]. However, TLS has also been reported in association with ionizing radiation, glucocorticoids, and monoclonal antibody therapy [21–23]. Patients with pre-existing compromised renal function are particularly at risk for developing TLS, since the kidneys are responsible for the excretion of the metabolic byproducts of rapid cell death caused by the therapeutic intervention. The heavy load of uric acid and potassium can lead to uric acid nephropathy and hyperkalemia with the formation of uric acid crystals in the renal tubules [24,25]. Precipitation of calcium phosphate salts may also contribute to and increase the risk of acute renal failure.

Since most patients with the diagnosis of CLL who have active disease requiring therapeutic intervention are treated as outpatients, it is important to call to the attention of the treating physician that TLS can occur acutely in association with nucleoside analogue therapy, and lead to critical, life-threatening complications requiring hospitalization and aggressive therapeutic intervention. In the case presented herein, allopurinol and sodium bicarbonate with hydration were not administered prior to and during the treatment cycle. Unfortunately, the patient developed TLS with acute renal failure with hyperkalemia and hyperuricemia, which required hemodialysis and prolonged hospitalization shortly after completion of the 5-day treatment regimen. Of the five cases of TLS associated with fludarabine therapy, including our case presented herein, all but one occurred after the first cycle of fludarabine therapy, and in all cases the symptoms and laboratory abnormalities occurred within the first week after completion of the administration of the drug. Also, in all cases fludarabine was the only agent used during the treatment cycle. In our search of the literature looking for TLS associated with the other purine analogues, i.e., cladribine and pentostatin, we found three cases. All three were associated with the administration of cladribine, and only one of the three reported cases occurred with the treatment of CLL [26–28].

TLS is an uncommon complication of the treatment of CLL, and only five cases associated with fludarabine therapy have been reported. However, it would seem prudent to initiate treatment with the addition of allopurinol, and encourage hydration with copious amounts of oral fluids during therapy. Since nucleoside analogues have become increasingly more popular and accepted standard therapy for the treatment of newly diagnosed, as well as previously treated symptomatic patients with CLL, it is likely that TLS associated with this therapy will be more frequently encountered.

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