Tumour lysis syndrome after treatment of chronic lymphocytic leukaemia with fludarabine

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Summary: Fludarabine is one of the most recent and promising therapeutic agents for chronic lymphocytic leukaemia. We describe a patient who developed tumour lysis syndrome after the first course of treatment with fludarabine and call attention to this uncommon but potentially lethal complication that has not been previously taken into account in this neoplasia. It should always be anticipated when patients are treated with new and effective drugs.

Introduction

Tumour lysis syndrome (TLS) can be anticipated in neoplasias in which chemotherapy is highly effective, but it has been an unexpected risk in the treatment of chronic lymphocytic leukaemia (CLL). However, the appearance of new drugs with a high cyto-reductive effect such as fludarabine phosphate (9-beta-D-arabinofuranosyl-2-fluoro-adenina 5'-phosphate) and other purine analogues raises the possibility of therapy-induced TLS in this condition. We report a patient with CLL who, after the first course of fludarabine, developed TLS with acute renal failure.

Case report

A 59 year old woman was diagnosed in 1982 as having CLL with RAI stage 0. Total lymphocyte count was 11 x 10^9/l, lymphocytes exhibited a monoclonal IgM-kappa and a mature lymphoid population occupied 90% of the bone marrow. The disease steadily progressed and in 1985 she was initially treated with monthly doses of chlorambucil and prednisone. In the last 2 years lymphadenopathy, splenomegaly and hepatomegaly progressed, and the doubling time of the lymphocyte count became very short (one month). She had lymph node enlargement in the cervical, supraclavicular, axillary and inguinal chains with several nodes about 2 x 2 cm, a 4 cm hepatomegaly and a 3 cm splenomegaly below the costal margins. Ultrasonography of the abdomen demonstrated retroperitoneal, paraortic and splenic hilum lymph node enlargement. Total lymphocyte count was 160 x 10^9/l, haemoglobin 14.2 g/dl, platelets 140 x 10^9/l and serum lactic dehydrogenase (LDH) level 673 U/l, uric acid 493 μmol/l and creatinine 91.9 μmol/l. She was classified as RAI stage II.

After taking into account the progression of the disease, the rapid doubling time of the lymphocyte count and the absence of response to chlorambucil, she was treated with fludarabine 30 mg/m2 for 5 consecutive days in the outpatient clinic. She did not receive prophylactic allopurinol. Two days after treatment she had left flank pain, oliguria, nausea and vomiting. Physical examination demonstrated a slight reduction of the lymphadenopathy and hepatosplenomegaly. The leucocyte count was 16 x 10^9/l, lymphocyte count 2.7 x 10^9/l and platelets 117 x 10^9/l. Serum creatinine was 866 μmol/l, urea 53 mmol/l, uric acid 2,974 μmol/l, phosphorus 9.81 mmol/l, calcium 1.45 mmol/l, potassium 9.8 mmol/l and total CO2 19.3 mmol/l. Urine sediment had only polymorphonuclear leucocytes. Ultrasonography demonstrated normal kidneys with no lithiasis. Haemodialysis was performed on admission and in the two following days with progressive normalization of chemical parameters. On discharge, serum creatinine was 123 μmol/l and uric acid 297 μmol/l. After prophylactic treatment with hydration, allopurinol and bicarbonate, a second and third course of therapy with fludarabine were administered and normal levels of biochemical parameters were documented throughout the course of therapy.

Discussion

TLS results from the massive destruction of tumour cells by an effective treatment. It can occur

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mainly in highly chemosensitive tumours, such as acute leukaemia, and lymphoblastic and high grade lymphomas. In these cases prophylactic treatment is mandatory to prevent acute renal failure. In low grade lymphoid neoplasias such as CLL, the reports of TLS have been anecdotal, as the tumour cell destruction is not rapid and effective, but slow and progressive. However, when intensive therapy has been used in CLL, isolated cases of TLS have been reported: a fatal one in a patient with prolymphocytic leukaemia after continuous low-dose vincristine and high-dose prednisone and four cases in eight patients with CLL treated with intensive therapy with high-dose Ara-C, cisplatin and etoposide. TLS occurred in three of these cases, despite prophylactic treatment but only one patient required haemodialysis.

Fludarabine has become one of the most promising agents in the treatment of CLL, as it can achieve a 59% remission rate in previously treated patients and 72% of complete remissions in untreated patients. The most important toxic effects are myelosuppression, infections and occasional central nervous system toxicity. Although fludarabine can produce rapid responses, TLS or severe renal insufficiency have not been reported, and prophylactic measures have not been specifically stressed in the major series referring to treatment of CLL or low grade lymphomas. Nevertheless, isolated cases of TLS have been reported by others.

TLS and renal failure not requiring haemodialysis developed in a previously treated CLL patient with low lymphocyte count (23.1 × 10⁹/l), generalized lymphadenopathy and marked splenomegaly after the first course of therapy. In the same paper two other CLL cases with a leucocyte count over 200 × 10⁹/l who developed TLS requiring haemodialysis are discussed. Two more TLS cases had been reported in CLL: one case in a German series of 19 patients treated with fludarabine and another one in a patient treated with a combination of fludarabine and chlorambucil. Although the leucocyte count is reduced in a substantial number of patients to under 10 × 10⁹/l after the first course of treatment, at which stage TLS could be expected, another case has been reported after the third course, suggesting an intense cytolytic response throughout the treatment.

As fludarabine is now available for use in Europe and is one of the first-line drugs for the treatment of CLL, it is of paramount importance to be aware that there is a risk of TLS both initially and throughout the treatment. We urge clinicians to arrange prophylactic measures with forced hydration, bicarbonate and allopurinol, and to make sequential controls of the biochemical parameters in every course of treatment in order to avoid this potentially lethal complication.

References

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