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Original Article

Tumor lysis syndrome in patients with chronic lymphocytic leukemia: two case reports and review of the literature

Yuqing Miao[1,2], Xiaoyan Qu[1], Li Wang[1], Lei Fan[1], Hao Xu[2], Wei Xu[1], Jianyong Li[1,3]

[1]Department of Hematology, First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, Jiangsu Province, China; [2]Department of Hematology, The First Ren Min Hospital of Yancheng, Yancheng, Jiangsu Province, China; [3]Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing Medical University, Nanjing 210029, China

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Abstract: Tumor lysis syndrome (TLS) is a rare complication during the treatment of chronic lymphocytic leukemia (CLL). Although TLS is unusual in CLL, it should not be overlooked as it is associated with high mortality. In the era of novel agents, there is greater concern that the incidence of TLS in CLL may occur more frequently. We herein reported 2 patients with CLL who developed TLS during treatment. One patient was alleviated after hydration, allopurinol and forced diuresis; and the other was relieved underwent hemodialysis because of oliguria. Both of them have some risk factors, such as increased lactate dehydrogenase, or bulky disease at diagnosis. Clinicians should put more emphasis on pretreatment risk factors, clinical awareness, close monitoring and early intervention, which are the keystones in the management of the patients with risk factors.

Keywords: Tumor lysis syndrome, chronic lymphocytic leukemia, risk factors

Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western countries, with more than 15000 cases recognized annually and resulting in almost 5000 cancer related deaths yearly in the United States [1]. Alkylating agents and purine analogues therapy was frequently reported effective as first-line treatment for decades. But in recent years, several novel agents have been developed or used in the clinic, including phosphatidylinositol 3-kinase inhibitors (idelalisib and IPI-145), Bruton tyrosine kinase inhibitors (ibrutinib), B cell lymphoma 2 inhibitors (ABT-263 and ABT-199), new anti-CD20 monoclonal antibodies (oftumumab, obinutuzumab), cyclin-dependent kinase inhibitors (flavopiridol and dinaciclib), immunomodulators (lenalidomide) and chimeric antigen receptor T-cell (CAR-T) therapy [2]. Because of the very active armamentarium to therapy, the incidence of tumor lysis syndrome (TLS) may be increasing, such as ABT-199 [3] or flavopiridol [4], and so on.

TLS, a life threatening emergency, is due to destruction and massive release of intracellular metabolites from tumor cells after the beginning of cytotoxic therapy [5], which often resulting in acute kidney injury (AKI) and sometimes requiring dialysis (AKI-D). Intracellular metabolites, coming from the major tumor cytoreduction, may cause severe hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia [5]. The syndrome usually occurs in patients with tumors highly sensitive to the cytotoxic agents employed, such as high-grade lymphomas and acute leukemias, but rare in CLL patients.

We report two cases of patients with CLL who developed TLS after treatment with fludarabine/cyclophosphamide and bendamustine, respectively. Both episodes of TLS were treated with allopurinol and alkalinization of urine with or without hemodialysis, and the blood biochemical parameters recovered in both cases. In this article, we summarized the current data on the occurrence of TLS in patients with CLL,

especially the risk factors and management of TLS.

Case 1

A 74-year-old female patient was diagnosed with CLL in November 2011 (immunophenotype: CD5+, CD19+, CD20+, CD22+, CD23+, dim expression of surface immunoglobulin kappa chain). The patient was at Rai stage III and received chemotherapy with fludarabine (30 mg/m^2) and cyclophosphamide (250 mg/m^2) on days 1-3. During the course of treatment, the patient had nausea and vomiting. The third day after chemotherapy, blood biochemical examination showed elevated urea nitrogen (BUN) 43.81 mmol/L (normal range: 2.1-7.2 mmol/L), creatinine 478.3 mmol/L (normal range: 44-96 mmol/L), lactate dehydrogenase (LDH) 1120 U/L (normal range: 109-245 U/L), phosphate 6.46 mmol/L (normal range: 0.9-1.34 mmol/L); potassium 6.27 mmol/L (normal range: 3.5-5.3 mmol/L), sodium 132.7 mmol/L (137-147 mmol/L) and decreased calcium 1.29 mmol/L (normal range: 2.15-2.55 mmol/L). She was complicated with TLS with acute oliguric renal failure.

We monitored her hyperkalemia closely and treated with insulin, glucose, diuretic and calcium gluconate. At the same time, we gave a sufficient hydration, urine alkalization and allopurinol. After a 14-day treatment, the creatinine fell to 105 mmol/L, and in a stable condition. The patient was discharged from the hospital and remained stable at six-month follow-up. The following chemotherapy process went smoothly without TLS.

Case 2

A 60-year-old female patient was diagnosed with CLL in February 2011 (immunophenotype: CD5+, CD19+, CD23+, CD20^{dim}, FMC7-). She did not received any treatment because of no therapeutic indications. Forty months later, in July 2014, the patient had disease progression with progressive lymph node enlargement (the right mandibular lymph node 10 cm in diameter) with the hearing loss of right ear. She received hydrochloride bendamustine treatment (100 mg/m^2 days 1-2). On day 4 after chemotherapy, blood biochemical examination showed elevated BUN 35.1 mmol/L, creatinine 555.4 mmol/L, LDH 233 U/L, phosphate 7.26 mmol/L; Potassium 5.96 mmol/L, sodium 133.4 mmol/L and decreased calcium 1.7 mmol/L. She was also exhibited TLS with acute oliguric renal failure.

Due to her poor general condition, refractory hyperkalemia and oliguria, we performed urgent hemodialysis. Simultaneously, the patient underwent aggressive fluid resuscitation and was given insulin, glucose and calcium gluconate for her hyperkalemia. Fortunately, oliguria and refractory hyperkalemia quickly improved. On the ninth day, her renal function recovered to normal. Two months later, the patient received the second course of bendamustine at dose of 50 mg/m^2 on days 1-2 and everything was smooth. The patient was treated with 5 cycles of hydrochloride bendamustine treatment without TLS, and with stable disease in the following 11 months.

Discussion

TLS is a collection of metabolic and electrolyte disturbances that can be observed during the destruction of tumor cells. High cellular proliferation and turnover result in hyperphosphatemia, hypocalcemia, hyperkalemia and hyperuricemia. Risk factors for TLS include high tumor burden, high rate of proliferation and disease that is highly responsive to therapy [6]. The common fatal consequences of the release of the contents of tumor cells include seizure, AKI and cardiac arrhythmia [7]. TLS is life-threatening, so early detection of high risk patients is essential [4].

According to the previous reports, TLS in CLL is rare with conventional chemo (immuno) therapies, such as 2-chlorodeoxyadenosine [8, 9], fludarabine [10-17], anti-CD20 monoclonal antibody [18, 19], bendamustine [15], Ibrutinib [20], corticosteroid [21, 22], as well as with aggressive combination chemotherapy regimens [23]. Cheson et al reviewed 6137 patients with CLL treated with fludarabine and found the morbidity and mortality of TLS were 0.33% and 20%, respectively [10]. TLS after fludarabine treatment of CLL is rare [10-17] and some cases developing TLS after fludarabine and cyclophosphamide combination has been reported [15].

The tumor-related predictors of risk of TLS is the type and burden of malignancy, which can

be stratified into three risk groups: a high risk group, an intermediate risk group, and a low risk group [24]. Low risk diseases include indolent lymphomas, CLL, chronic myeloid leukemia in the chronic phase, AML with WBC count < 25000/ml and an LDH elevated to less than twice ULN, multiple myeloma, and solid cancers. According to Mirrakhimov et al's analysis, when assessing the risk of TLS in a particular patient, it is essential to bear in mind both the general and tumor-related predictors of risk [25]. The general risks included advanced age, adenopathy ≥ 10 cm, splenomegaly, volume depletion, the use of medications capable of detrimentally affecting renal function, baseline kidney disease, a baseline increase in serum uric acid, phosphorus, potassium, LDH and general comorbid conditions. The risk factors of our case 1 were the age and an elevated LDH, and the risk factor of case 2 was bulky with hepatosplenomegaly and lymph node greater than 10 cm. We speculated that both of our patients had a sensitivity to the therapy.

It is essential to remember that the prevention of TLS is more important and cost-effective than the treatment of it. Currently, the main management of TLS includes monitoring of electrolyte abnormalities, vigorous hydration, urine alkalinization, using of diuretics, prophylactic antihyperuricemic therapy with allopurinol, and rasburicase treatment of patients at high-risk or with established hyperuricemia. Urine alkalinization and use of diuretics remain controversial in clinical practices [7]. Allopurinol decreases the new production of uric acid (UA) by inhibiting enzyme xanthine oxidase and blocking oxidation of xanthine and hypoxanthine into UA [7, 26]. Therefore, following allopurinol administration, there is a time lag for reduction in UA levels. Rasburicase, a recombinant urate oxidase, rapidly reduces UA by catalyzing the conversion of the existing pool of UA into allantoin which is 5-10 times more soluble in urine than UA [27]. Rasburicase is effective in reducing serum UA levels in adults with TLS but at a significant cost, and evidence currently is lacking in adults to report whether rasburicase use improves clinical outcomes compared with other alternatives [28]. In spite of intravenous hydration during chemotherapy and increased oral fluid intake, the two patients developed TLS after treatment. Fortunately, both cases recovered with allopurinol therapy, alkalinization of urine, with hemodialysis or not. During the subsequent cycles of chemotherapy, TLS and renal failure were prevented by a lower dose of chemotherapy, increased intravenous hydration, the prophylactic administration of allopurinol and sodium bicarbonate.

In general, due to the improved efficacy and survival rates of patients with the novel agents used in CLL, the incidence of TLS increased but still extremely rare. Being a life threatening emergency, greater caution should be exercised to avoid TLS especially in patients who are sensitive to chemotherapy with known pretreatment risk factors, including renal impairment, bulky, hyperuricemia, and increased LDH et al.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiaoyan Qu, Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, 300 Guangzhou Road, Nanjing 210029, China. Tel: 86-25-68136034; Fax: 86-25-83781-120; E-mail: quxiaoyan205@163.com; Dr. Hao Xu, Department of Hematology, The First People's Hospital of Yancheng, 16 Yuehe Road, Yancheng 224006, China. Tel: 86-515-88508849; Fax: 86-515-88508910; E-mail: xhxuhao2008@163.com

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