

Case Report

Adult high-risk Burkitt's acute lymphocytic leukemia was successfully rescued by rituximab combined with hyper-CVAD/MA regimens: two case reports and a literature review

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Abstract: Objective: We report two adult cases with high-risk Burkitt's acute lymphocytic leukemia (Burkitt's ALL) was successfully rescued by rituximab combined with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone)/MA (methotrexate and cytarabine) regimens. Methods: Two patients were diagnosed with high-risk Burkitt's ALL. One had a t(8;22) chromosome translocation, respiratory failure, pulmonary infection, pleural effusion, hypoproteinemia, and his LDH was 13854 U/L; he developed central nervous system leukemia shortly thereafter. Another patient had a t(8;14) chromosome translocation and was two months pregnant, and her LDH was 5664 U/L. They both initially received low-dose prephase chemotherapy followed by rituximab combined with a hyper-CVAD chemotherapy regimen. Results: Both patients achieved complete remission after a course of chemotherapy; the cerebrospinal fluid of patient one returned to normal levels after administration of methotrexate by intrathecal injection and high-dose MA chemotherapy. His lung infection gradually improved, and multiple high-density bilateral pulmonary plaques has been absorbed. The second patient safely underwent a medical abortion after her blood cell count returned to normal levels. Both patients are currently receiving an alternative chemotherapy regimen consisting of rituximab combined with hyper-CVAD/MA. Conclusion: Burkitt's ALL is a medical emergency and should be promptly diagnosed and treated with proper chemotherapy. Rituximab combined with hyper-CVAD/MA regimens may be an effective therapeutic strategy for patients to achieve the chance of survival.

Keywords: Burkitt, acute lymphocytic leukemia, *MYC* arrangement, t(8;14), t(8;22)

Introduction

Burkitt's lymphoma/leukemia (BL) is a rare and aggressive mature B-cell non-Hodgkin's lymphoma (NHL) that was first diagnosed in African children in the late 1950s, with an incidence of approximately 1% for mature NHL [1, 2]. The three established subtypes of BL are endemic, sporadic and AIDS-related BL. BL is more common in whites and males than in other race groups and females [3]. BL also correlates with age, the incidence of BL gradually decreases from 38% in patients aged 1-14 years old to 21% in patients aged 15-19 years and 5% in patients older than 20 years [3]. Translocations involving the *MYC* gene on chromosome 8 to its

partner chromosomes, including chromosome 2 [t(2;8), 15%], chromosome 14 [t(8;14), 80%] and chromosome 22 [t(8;22), 5%], occur in almost all patients with BL [4]. Most cases of BL present with tumor masses, and bone marrow (BM) involvement is common. Rarely, BL involves only the BM, which was previously referred to "L3" acute lymphocytic leukemia (ALL-L3) [5]. BL patients with BM involvement are classified to Ann Arbor IV stage and thought to have very poor survival, the estimated median progression-free survival (PFS) and overall survival (OS) were only 3 and 5 months [6].

In this article, we present the two adult cases diagnosed with sporadic high-risk Burkitt's ALL.

Rituximab-based chemotherapy in Burkitt's ALL

One patient had a rare t(8;22) chromosome translocation and respiratory failure, whereas another female patient had a t(8;14) chromosome translocation and was two months pregnant. Both patients were successfully rescued by rituximab combined with Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone)/MA (methotrexate and cytarabine) regimens. We also retrospectively introduce data from the two patients and review the related literature.

Materials and methods

History of present illness

Informed consent was obtained before treatment, and the institutional review board approved this case report.

Case one was a 46-year-old man. He was admitted to our hospital on February 7th, 2017 due to "fever (37.7-38.5°C) and dizziness for a week, shortness of breath for one day". The patient developed a slight cough with sputum. No skin hemorrhage or ecchymosis was found. The blood cell count revealed the following: the white blood cell (WBC) count was $33.84 \times 10^9/L$ (normal range, $4-10 \times 10^9/L$) with 50% blasts, the hemoglobin (Hb) level was 66 g/L (normal range, 120-160 g/L), and the platelet (PLT) count was $20 \times 10^9/L$ (normal range, $100-300 \times 10^9/L$). The patient was admitted due to suspected acute leukemia. Since onset, the patient was in poor spirits, had poor appetite and sleep, and had lost a significant amount of weight.

Case two was a 16-year-old female who was two months pregnant. She was admitted to our center on April 10th, 2017 due to a "neck mass for two weeks". Fever, cough and skin hemorrhage were absent. The blood cell count showed the following: the WBC count was $29.46 \times 10^9/L$ with 65% blasts, the Hb level was 106 g/L, and the PLT count was $29 \times 10^9/L$. The patient was admitted due to suspected acute leukemia. Since onset, the patient was in normal spirits, exhibited normal appetite and sleep, and had not lost significant amounts of weight.

Past history: The two patients had no history of hepatitis, tuberculosis or other infectious diseases, no history of food or drug allergy, no history of trauma surgery, and no history of blood transfusion.

Personal history: The two patients had no history of contact with contaminated water, no history of smoking, drinking or other unhealthy habits, and no history of contact with patients with acquired immunodeficiency syndrome (AIDS). In addition, the family history did not identify notable diseases.

Physical examination: Patient one exhibited severe shortness of breath but a lucid mental status, moist rales in both lungs, an increased heart rate (114 beats/minute), and mild edema in both lower extremities. Neither enlarged superficial lymph nodes nor liver and spleen could be palpated. Patient two had enlarged lymph nodes in her left neck and an enlarged spleen (3 cm below the left costal margin). Cardiac and pulmonary abnormalities were not detected. The liver could not be palpated below the right costal margin.

Adjuvant examinations

Patient one: the blood cell count showed a WBC of $33.84 \times 10^9/L$ with 50% blasts, a Hb level of 66 g/L, a PLT count of $20 \times 10^9/L$. An albumin (ALB) level of 22.0 g/L (normal range, 40-55 g/L), a triglyceride (TG) level of 3.63 mmol/L (normal range, 0-1.7 mmol/L), and a lactate dehydrogenase (LDH) level of 13854 U/L (normal range, 0-248 U/L). A blood gas analysis showed respiratory failure (PO_2 56 mmHg, PH 7.25, and PCO_2 30 mmHg). The prothrombin time (PT) was 14 s (normal range, 9.8-12.1 s), the activated partial prothrombin time (APTT) was 18.1 s (normal range, 21.1-36.5 s), and the thrombin time (TT) was 18.0 s (normal range, 14.0-21.0 s). The fibrinogen (Fbg) level was 7.16 g/L (normal range, 1.8-3.5 g/L). The serum ferritin (SF) level was 3000 $\mu g/L$ (normal range, 30-400 $\mu g/L$). The procalcitonin (PCT) level was 2.25 ng/mL (< 0.5 ng/mL), and the C-reactive protein (CRP) level was 84.5 mg/L (normal range, 0-8 mg/L). In addition, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) DNA serological tests, a blood culture (veins in both upper limbs, cultures for aerobic, anaerobic and fungal, three times), a (1-3)-Beta-D-Glucan assay (G test) and a galactomannan assay (GM test) were all negative. The alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (BIL), and serum creatinine (Scr) values were all normal. A computed tomography (CT) scan examination revealed bilateral high-density plaques in the

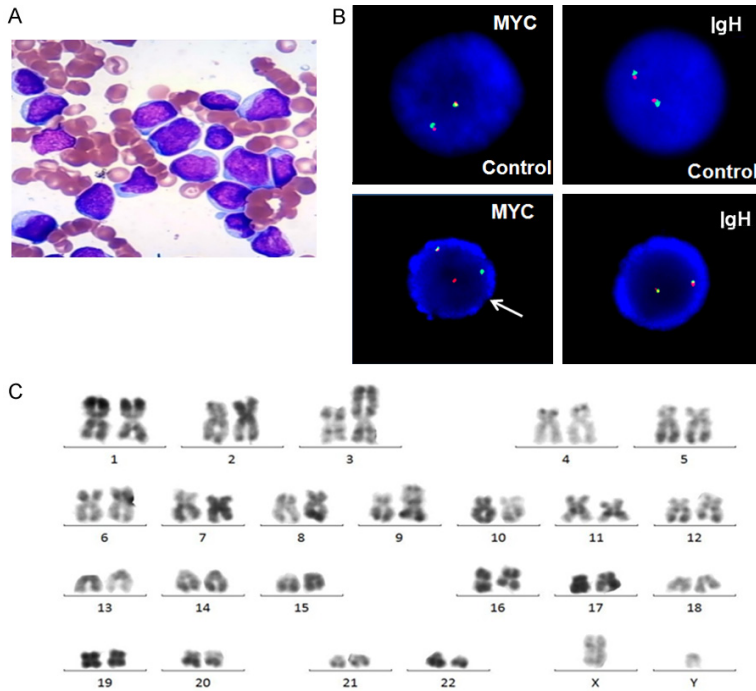


Figure 1. The bone marrow morphology, molecular genetic abnormalities and chromosome karyotype in patient one. A. The bone marrow morphology showed acute lymphoblastic leukemia (Wright-Giemsa staining, $\times 1,000$). B. *MYC* gene rearrangement (arrow cells with *MYC* gene rearrangement showed one red, one green and one yellow signal; normal cells showed two yellow signals) was detected by fluorescence in situ hybridization (FISH), but *IgH* gene rearrangement was not detected (Normal cells showed two yellow signals). C. Chromosome karyotyping indicated 46, XY, add(3)(p26), t(8;22)(q24;q11), and add(9)(p22)[9].

lung, bilateral pleural effusion and an enlarged spleen. Electrocardiogram (ECG) prompted sinus tachycardia. Echocardiography showed that the left ventricular ejection fraction was 66%, and a BM smear confirmed ALL, with 90% abnormal lymphocytes (**Figure 1A**). Flow cytometry showed that 83.5% of the abnormal cells expressed HLA-DR, CD19, CD20, CD38, cCD79a, CD22, cKappa, cIgM, CD10 and sIgM, and these cells were negative for cLambda, CD34, CD117, CD7, CD33, CD13, CD15, CD64, CD56, CD4, CD14, CD36, TDT, MPO, cCD3 and CD5. The BCR/ABL fusion gene was not detected. Furthermore, *MYC* gene rearrangement was detected in 79% of cells by fluorescence in situ hybridization (FISH), but immunoglobulin heavy chain (*IgH*) gene rearrangement was not detected (**Figure 1B**). Chromosome karyotyping indicated 46, XY, and add(3)(p26), t(8;22)(q24;q11), add(9)(p22)[9] (**Figure 1C**), and BM pathology supported B-ALL which positively expressed CD20, CD10 and PAX5, whereas

CD3, CD7, CD34, CD117 and TDT were negative.

Patient two: the blood cell count showed the following: a WBC of $29.46 \times 10^9/L$ with 65% blasts, a Hb level of 106 g/L, a PLT level of $29 \times 10^9/L$. An ALT level of 99 U/L, an AST level of 92 U/L, and a LDH level of 5664 U/L. The PT, APTT, TT and Fbg were normal. In addition, the SF, PCT, CRP, EBV and CMV DNA serological tests, blood culture, G test and GM test were all negative. A color ultrasound revealed many enlarged lymph nodes throughout the body and splenomegaly. A CT scan examination revealed normal bilateral pulmonary morphology and an enlarged spleen. ECG and echocardiography results were normal. A BM smear showed ALL with 81% abnormal lymphocytes (**Figure 2A**), and flow cytometry showed 77.9% of the abnormal cells expressed HLA-DR, CD19, CD20, Kappa, and CD10, whereas they were negative for CD34, CD-

117, CD7, CD33, CD13, CD15, and CD2. The BCR/ABL fusion gene was not detected. Furthermore, 25% of *MYC* gene rearrangement, 30% of *IgH* gene rearrangement and 20% of *MYC/IgH* gene translocation were detected by FISH (**Figure 2B**). *BCL-2* and *BCL-6* gene rearrangements were not detected. Chromosome karyotyping indicated 46, XX, and dup(1)(q21q24),t(8;14)(q24;q32)[7]/46,XX[5]. BM pathology tests supported B-ALL: CD20 (2+), CD79a (2+), CD10 (2+), mum-1 (1+), Ki-67 (100%), whereas CD2, CD3, CD7, CD33, CD34, CD56, BCL-6, TDT were negative.

Diagnosis and treatment course

Based on the above findings, patient one was clinically diagnosed with Burkitt's ALL with t(8;22) chromosome translocation, respiratory failure, pulmonary infection, pleural effusion and hypoproteinemia. He initially received low-dose prephase chemotherapy (cyclophospha-

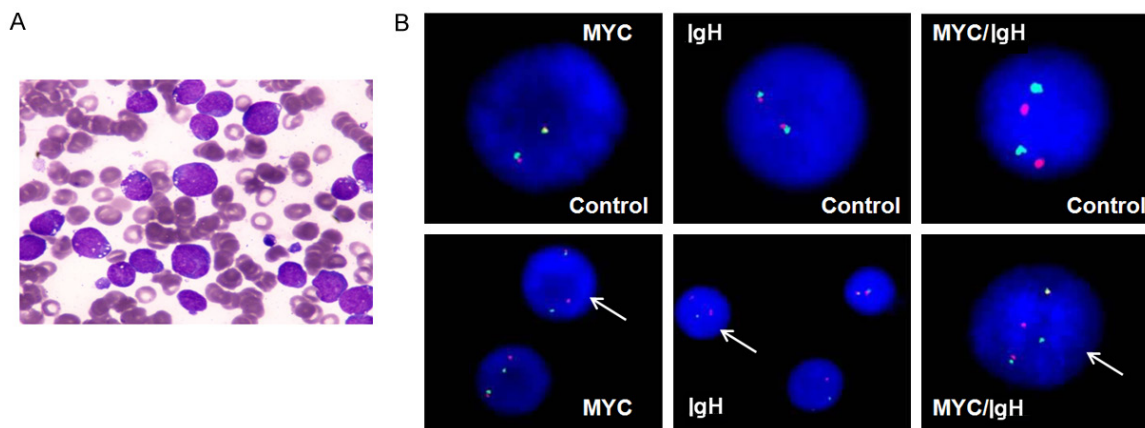


Figure 2. The bone marrow morphology and molecular genetic abnormalities in patient two. A. Bone marrow morphology showed acute lymphoblastic leukemia with cytoplasmic vacuoles in the abnormal lymphocytes (Wright-Giemsa staining, $\times 1,000$). B. *MYC* gene rearrangement (arrow cells with *MYC* gene rearrangement showed one red, one green and one yellow signal; normal cells showed two yellow signals) was positive; *IgH* gene rearrangement (arrow cells with *IgH* gene rearrangement showed one red, one green and one yellow signal; normal cells showed two yellow signals) was positive; and *MYC/IgH* gene translocation (arrow cells with *MYC/IgH* gene translocation showed one red, one green and two yellow signals; normal cells showed two red and two green signals) was positive by FISH.

mide, 300 mg/d and prednisone, 60 mg/d, d 1-3) followed by rituximab combined with a hyper-CVAD chemotherapy regimen (rituximab, 375 mg/m² at d 1; cyclophosphamide, 300 mg/m² at d 2-4; vincristine, 1.4 mg/m² at d 5, 12; doxorubicin, 16.6 mg/m² at d 5-7; dexamethasone, 40 mg/m², at d 2-5, d 12-15), anti-infection drugs treatment (Imipenem/cilastatin, vancomycin hydrochloride and voriconazole) and blood component infusions. His lung infection gradually improved, his body temperature decreased to normal level, and multiple bilateral pulmonary high-density plaques had been absorbed (**Figure 3A and 3B**).

Patient two was also clinically diagnosed with Burkitt's ALL with t(8;14) chromosome translocation, and she was two months pregnant. She received the same prephase chemotherapy and rituximab combined with a hyper-CVAD chemotherapy regimen (the dosage was the same as described for the above patient), anti-infection drugs treatment (cefoperazone and sulbactam) and blood component infusions. After her blood cell count returned to normal levels, she successfully and safely underwent a medical abortion.

Results

Patient one: after a course of chemotherapy, a BM smear showed that Burkitt's ALL was complete remission (CR), and the proportion of BM

minimal residual disease (MRD) was 0.14%. The blood cell count showed a WBC of $5.01 \times 10^9/L$, a Hb level of 88 g/L, and a PLT level of $617 \times 10^9/L$. However, the patient developed central nervous system (CNS) symptoms in the following days, including a crooked mouth and pattern disappearance on the left side of the face. Flow cytometry detected that 91.48% of the abnormal cells expressed CD10+HLA-DR+CD19+CD20+CD45+ in his cerebrospinal fluid, and he was consequently diagnosed with CNS leukemia. After treatment of methotrexate by intrathecal injection and high-dose MA (methotrexate, 1.5 g/m² at d 1 and cytarabine, 3.0 g/m², 4 doses, d 3-4) chemotherapy by intravenous infusion, his cerebrospinal fluid returned to normal levels. The patient is currently in CR, and the MRD in his BM and cerebrospinal fluid is negative. The patient is still undergoing rituximab combined with hyper-CVAD/MA alternative chemotherapy due to no suitable donor for allogeneic-hematopoietic stem cell transplantation (allo-HSCT).

Patient two: after a course of chemotherapy, her blood cell count returned to normal, and a BM smear showed that Burkitt's ALL was in CR; the MRD in her BM was negative. She subsequently received an intrathecal injection of methotrexate and cytarabine to prevent CNS leukemia, and her cerebrospinal fluid was normal. The same as the patient one, patient two is currently undergoing rituximab combined

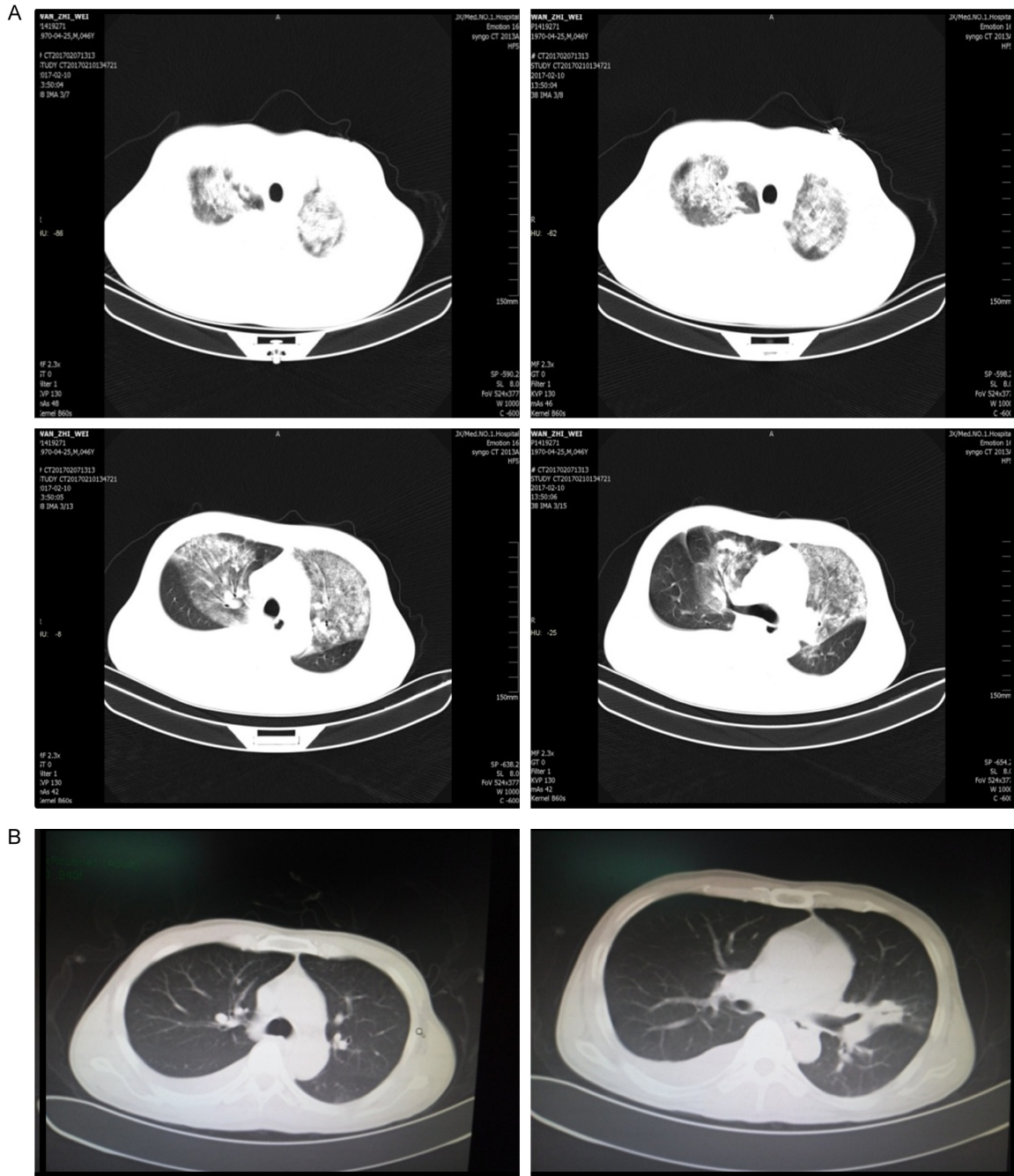


Figure 3. The results of computed tomography (CT) scans at the onset and after one course of chemotherapy in patient one. A. Bilateral high-density pulmonary plaques and bilateral pleural effusion at the onset. B. Multiple bilateral pulmonary high-density plaques had been absorbed after one course of chemotherapy.

with hyper-CVAD/MA alternative chemotherapy regimens due to donor limitation for allo-HSCT.

Discussion

BL is a highly aggressive mature B-cell neoplasm characterized by the deregulation of the *MYC* gene. BL is often thought as a childhood

disease with a 5-year overall survival of approximately 90% when treated with intensive chemo-immunotherapy (e.g., R-Hyper-CVAD or CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine)) [7]. However, over half of BL cases in the US occur in adults over 40 years of age, and survival is shorter than in young

patients [8]. Burkitt's ALL is a rare type of adult ALL clinically characterized by high cell proliferation and high LDH, and it tends to involve the CNS at diagnosis or early in the disease course. In addition, initial chemotherapy easily leads to a risk of severe acute tumor lysis syndrome, which is associated with high mortality. Thus, Burkitt's ALL is a medical emergency and a life-threatening disease, and prompt diagnosis and treatment are crucial to avoid a fatal outcome. Herein, we report two adult cases with sporadic high-risk Burkitt's ALL. One patient initially presented with respiratory failure and a pulmonary infection, whereas another patient was two months pregnant at the time of diagnosis. Both patients successfully achieved CR after a timely diagnosis and low-dose prephase chemotherapy followed by rituximab combined with a hyper-CVAD regimen.

The discovery of the t(8;14) chromosome translocation, which results from the translocation of the *MYC* gene locus on chromosome 8 and *IgH* locus on chromosome 14, is a hallmark of BL and is observed in 80% of BL patients [9]. Fifteen percent and 5% of cases have translocations involving the κ light chain gene on chromosome 2 (t(2;8)) or the λ light chain gene on chromosome 22 (t(8;22)), respectively [4]. Additional genetic abnormalities have been reported, such as the *CCND3* gene, which encodes *cyclin D3* to regulate the G 1 to S transition during the cell cycle (seen in 38% of patients with sporadic BL) [10], inactivating mutations in *CDKN2A*, which encode *p16* (17%) and *TP53* (35%) [10, 11], the downregulation of the pro-apoptotic protein Bim 19, and mutations involving *TCF-3(E2A)* and/or its negative regulator *ID3* [12]. The morphological and histopathological characteristics of abnormal cells include the following: intermediate to large neoplastic cells in the BM, a basophilic cytoplasm, cytoplasmic vacuoles with a "starry sky" appearance, and multiple nucleoli. The Ki67 index is usually > 95%. Immunohistochemistry showed that BL cells are positive for sIgM and surface light chains ($\kappa > \lambda$), CD19, CD20, CD22, CD79a, CD10, BCL6, HLA-DR and CD43, and negative for CD5, BCL-2, TdT and CD23 [13].

Two diseases need to be differentiated: diffuse large B-cell lymphoma (DLBCL) and B-cell lymphoma unclassifiable, with features intermediate between BL and DLBCL (B-UNC/BL/DLBCL). DLBCL patients exhibit heterogeneous disease

with larger cells, Ki-67 index is usually < 90%, and tumor cells express CD19, CD20, CD22 and CD79a. Moreover, 60%-70% of time are BCL6 positive, whereas BCL2, CD10, CD5, CD30 and CD5 expression are variable. Some patients with very poor survival exhibit "double hit" cytogenetics with coincident *MYC* and *BCL-2* translocations or *MYC* and *BCL-6* translocations [14]. Patients with B-UNC/BL/DLBCL present with intermediate to large neoplastic cells, an intermediate Ki67 index that is usually between the levels observed in BL and DLBCL, and tumor cells that express CD19, CD20, CD33, CD79a, CD10 and BCL2; BCL6 expression is variable, and "double hit" cytogenetics involving *MYC* and another locus (*BCL2* accounting for 30%-50%) [15]. Gene expression profiling and micro-RNA profiles can distinguish BL from DLBCL based on a high level *c-MYC* target gene expression and low expression levels of major-histocompatibility-complex class I genes and NF- κ B genes in BL [4].

To date, we recognize three distinct subtypes of BL: endemic (African) BL, sporadic BL, and immunodeficiency-associated BL. According to the UKLG risk score, patients with BL/BLL are classified to two categories: low-risk (normal LDH and a single focus of disease measuring less than 10 cm) and high-risk (all other cases) [16]. In the past, leukemia restricted to the marrow and blood at the initial presentation was referred to as ALL-L3. Previous reports have indicated the median age and survival of patients with ALL-L3 to be 33.5 years and only 5.1 months, respectively [5]. Given the rapid doubling time of these leukemia cells, spontaneous tumor lysis (elevated uric acid level, hyperphosphatemia and hyperkalemia) and high serum LDH levels are common, and this disease easily involves the CNS. Sporadic Burkitt's ALL is a medical emergency with high early mortality, especially for high-risk patients [17]. Prompt diagnosis and treatment are crucial to avoid a fatal outcome and allow the possibility of subsequent therapy.

Due to a lack of large-sample, randomized and controlled studies, a uniform optimal regimen for Burkitt's ALL has not yet been defined. Compared with other types of ALL, the principles of Burkitt's ALL treatment include the following: 1. A low-dose prephase chemotherapy to prevent acute tumor lysis syndrome; 2. Multi-agent chemotherapy using high-dose cyclo-

phosphamide, anthracycline, high-dose MTX, and high-dose Arac for a short and intensive treatment regimen (6 to 8 courses) without maintenance; and 3. Early intensive CNS treatment, including multiple triple intrathecal injections, high-dose MTX, and high-dose Arac or cranial irradiation [18]. One study reported the long-term results in patients younger than 21 years with BL or DLBCL using the National Cancer Institute (NCI) 89-C-41 protocol (CODOX-M or CODOX-M/IVAC regimens) [19]. Among the 35 patients entered in the study, 32 (91%) achieved CR, and the 5-year OS and event free-survival (EFS) rates were 83% and 80%, respectively. Twenty-six newly diagnosed adult Burkitt's ALL patients who received the Hyper-CVAD regimen at the MD Anderson Cancer Center achieved a CR rate of 81%. The 3-year survival rate was 77% for patients younger than 60 years and 17% for patients 60 years or older ($P < 0.01$) [20]. In 2007, updated results from the MD Anderson Cancer Center showed that the addition of rituximab improved the OS of BL patients. Specifically, 31 patients with BL, atypical BL and B-ALL were treated with rituximab plus hyper-CVAD, which was alternated with rituximab plus MA. The overall response rate (RR) was 97% (CR rate, 86%), and the estimated 3-year OS, disease-free survival, and EFS rates were 89%, 88% and 80%, respectively. Toxicity was mainly hematologic and significant, but the toxicity was expected [21].

The roles of auto or allo-HSCT in adult BL and Burkitt's ALL are controversial. In a multicenter phase II study (HOVON27 BL study) in 27 newly diagnosed patients with BL/BLL who received high-dose induction chemotherapy followed by BEAM and auto-HSCT, the CR rate was 81%, the partial response (PR) rate was 11%, and the 5-year estimated OS and EFS were 81% and 73% [22]. Another study evaluated the role of HSCT in patients aged ≤ 18 years with refractory or recurrent Burkitt's ALL ($n=41$); the 5-year EFS (31% vs. 27%) and the probability of progressive disease (63% vs. 65%) were similar after allogeneic ($n=27$) and autologous ($n=14$) HSCT [23]. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) between 1985 and 2007 showed the outcomes for 241 BL patients after auto or allo-HSCT. For auto-HSCT, the OS at 5 years was 83% in CR1 and 31% for non-CR1. The PFS was 78% and 27% for CR1 and non-CR1, respectively. For allo-HSCT, OS at 5 years was 53% and 20% for the CR1 and non-CR1 while PFS

was 50% and 19%, respectively. In high-risk patients, allo-HSCT resulted in 27% of 5-year PFS [24]. However, due to a small sample size, we were unable to demonstrate the superiority of donor type (autologous vs. allogeneic) for patients with BL, which needs to be delineated in a future study.

In general, BM involvement, a complex karyotype and older age are poor predictors for PFS and OS in BL patients [6]. However, we did not examine the differences of survival time between BL patients with BM involvement and Burkitt's ALL only involving the BM. A study analyzed 23 patients, which included 10 patients with PBL (pure Burkitt's leukemia) and 13 patients with BL (Burkitt's lymphoma/leukemia with a tumor mass and marrow involvement). Complex karyotypes were observed in all patients with BL (100%) compared to the PBL group (40%; $P=0.061$). Patients with PBL had a significantly better 5-year OS (87.5% vs. 24.3%) than patients in the BL group ($P=0.005$) [25]. In our article, both patients initially presented with ALL-L3 and very high levels of LDH, i.e., 13854 U/L and 5664 U/L, which classified them as high-risk patients. Patient one had a severe pulmonary infection and respiratory failure, and patient two was two months pregnant. After our timely diagnosis and low-dose prophase chemotherapy followed by rituximab and hyper-CVAD/MA chemotherapy regimens, both patients achieved CR. In addition, patient two underwent a successful medical abortion after her blood cell count had normalized. Now, the survival time of both patients is more than ten months. However, they don't receive allo-HSCT due to the donor limitations.

In summary, Burkitt's ALL is a rare type of adult ALL characterized by high cell proliferation and high LDH, and this disease tends to involve the CNS and poses a high risk for severe acute tumor lysis syndrome and high mortality. In the clinic, Burkitt's ALL should be treated as a medical emergency and promptly diagnosed for administering proper chemotherapy. Rituximab combined with hyper-CVAD/MA chemotherapy regimens may be an effective therapeutic strategy prior to HSCT for high risk patients.

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Disclosure of conflict of interest

None.

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