Clinical Features and Treatment Strategies of Precursor B-cell Lymphoblastic Leukemia with C-myC Rearrangement in Childhood

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Abstract

Background: "Rare cases of Burkitt leukemia/lymphoma (BL) exhibiting a precursor B-cell phenotype (termed herein pre-BLL) were admitted by WHO Classification of Hematopoetic and Lymphoid Tissue, recent evidence suggests that these neoplasms genetically and epigenetically resemble precursor B-cell leukemia/lymphoma (pB-acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL)/LBL) rather than BL. The clinical features and treatment of childhood pre-BLL with C-myC rearrangement are poorly understood. Methods:The clinical features, treatment strategies and follow-up information of 9 cases with pre-BLL diagnosed by Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine from 2011 to 2020 were retrospectively analyzed. Results: All the 9 cases were confirmed to be pre-BLL by flow cytometry and fluorescence in situ hybridization, morphological classification were L2/L3, immunophenotype was CD10, CD19 positive, CD20, TDT, CD34 selective expression, sIgM negative, Kappa and Lambda light chain negative. Most of the pre-BLL cases were accompanied by elevated lactate dehydrogenase (LDH), uric acid levels. 5 cases received intensive chemotherapy with overlapping regimen, and all achieved sustained remission except for 1 case relapse and death. Among the 4 cases who received low-intensity chemotherapy for acute lymphoblastic leukemia, 2 cases died due to early relapse of the disease. Conclusions: Pre-BLL cases are rare. and intensive chemotherapy treatment according to protocols for mature B-cell NHL. Currently, the treatment strategies are still controversial. Considering the small number of cases, multi-center clinical studies should be actively carried out to find a standard treatment plan.

1 $_{I}$*NTRODUCTION*

The rearrangement of the c-MYC gene is the hallmark of Burkitt leukemia (BL), which is a kind of mature B-cell neoplasms, accounting for about 2% of acute pediatric leukemia. The well characterized immunophenotype for BL is mature B cell phenotype, including CD10, CD19, CD20, CD22, CD79a and sIgM, without the expression of CD34 and terminal deoxynucleotidyl transferase (TdT) [1, 2]. Except for BL, c-MYC rearrangement can also occur in other B-cell NHL, such as diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM) and so on[3]. Nevertheless, c-MYC rearrangement is also occasionally detected in acute lymphoblastic leukemia (ALL) with an immature B cell immunophenotype of B cell precursor (BCP-ALL). Although the "WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue" has noted these rare cases of BL exhibiting a precursor B-cell phenotype (termed herein "pre-BLL"), the characteristics of it are poorly understood for its rarity[4]. Because of the overlapping features between BL and pre-BLL, the diagnosis is often delayed and the treatment is controversial, making the clinical management complicated. In order to clarify

the clinical and biological characteristics and the treatment outcome of pre-BLL, we report nine patients with pre-BLL in this study.

2 $_{P}ATIENTSANDMETHODS$

Patients with pre-BLL included in this study were diagnosed and treated in the Shanghai Children's Medical Center (SCMC) from January 2001 to December 2020. The diagnosis was determined by cell morphology, flow-cytometric and molecular biologic analysis. The diagnostic criteria were based of French–American–British (FAB) classification and European Group for the Immunological Characterization of Leukemias criteria[5, 6]. The presence of c-MYC arrangement was confirmed by fluorescence in situ hybridization (FISH). Patient data analyses included basic clinical information: gender, age and extramedullary infiltration; laboratory information: white blood cell count, serum UA, LDH level; and details of treatments and outcomes. This study was approved by the institutional review board of the SCMC.

3 $_{R}ESULTS$

3.1 $_{C}linicalcharacteristicsofpatientswithpre-BLL$

Among all the patients with BCP-ALL diagnosed in SCMC from January 2001 to December 2020, nine were identified to carry c-MYC rearrangement. Two of the nine patients were [?] 10 years old (22%), while the other seven were $<$ 10 years old (78%), with a mean age of 6.8 years (1.5-12.8), close to the average onset age of pre-BLL of 6.1 years[7]. And there were 4 male children (44%) and 5 female children (56%). Alongside a mature B-cell immunophenotype, patients with BL usually have FAB-L3 morphology, and bulky disease, elevated LDH and UA, at the high risk of tumor lysis[8]. Cytomorphologic features showed that three of nine patients had FAB-L3 morphology (3/9), four of nine patients had FAB-L2 morphology (4/9), and the other two are not classifiable (2/9). Immunophenotypically, leukemia blasts were uniformly stained for CD10 (9/9), CD19 (9/9) and HLA-DR (9/9). The expression of TdT (6/9), CD34 (1/9), CD20 (3/9) and cμ (1/9) was variable. All the patients lacked the expression of sIgM and negative for kappa/lambda. The white blood cell counts at diagnosis were variable (mean 44,009/mm^3; range 710-199,450/mm^3). All but one patient had markedly increased serum LDH three times higher than baseline. One of nine patients had bulky disease (1/9). Liver and/or spleen (5/9) and lymph nodes (5/9) were frequently affected. Two patients had central nervous system (CNS) involved (2/9). In addition, one patient had other organs involved, including kidney, pancreas and intestinal wall. The patient with kidney involved was accompanied by renal failure and continuous renal replacement therapy (CRRT) was used at the initial stage of chemotherapy. Tumor lysis syndrome was encountered in induction chemotherapy by two patients, and were corrected soon (Table 1).

3.2 $_{T}reatmentsandoutcomes$

Four preBLL patients were initially treated according to B-NHL/ALL protocols for mature B-cell leukemia from the beginning. Two courses of rituximab were administered to one of them because of the early termination of therapy for recurrent intracranial fungal abscess.

One patient received induction treatment according to protocols for BCP-ALL for 71 days and switched to B-NHL/ALL courses. In three patients, intensive treatment was followed by ALL-type maintenance therapy. Relapse occurred in one patient after 5 months since diagnosis, and the other four patients had maintained completed remission (CR) until the last follow-up. The other four patients were treated according to BCP-ALL protocol[9], and two of them relapsed after 7 months and 19 months since diagnosis, respectively (Figure 1).

4 $_{D}ISCUSSION$

C-MYC has been described as a proto-oncogene that is involved in the pathogenesis of many

cancers, including leukemia and lymphoma. Physiologically, c-MYC plays an important role in B-cell differentiation and proliferation. During the maturation of B cell, c-MYC base levels are maintained and its transient downregulation is required at some specific point to promote the proliferation of B-cell[10, 11]. The most common c-MYC rearrangement is reciprocal chromosomal translocation between 8q24 and 14q32, followed by 8q24 with t(8;22)(q24;q11), and t(2;8)(p12;q24)[12]. The translocation places the c-MYC gene under direct regulation of the enhancer of the IGH (or IGK/IGL genes), causing overexpression of c-MYC gene[13].

Although it is mainly observed in mature B-cell neoplasms, c-MYC gene rearrangement can occasionally detected in patients with BCP-ALL immunophenotype. Previous published researches have shown that pre-BLL is a rare subtype comprising 0.1% (5/5280) of BCP-ALL in the Pediatric Oncology Group (POG) and 0.2% (10/4043) in a nationwide study in Japan[14, 15]. Our data also indicates that pre-BLL is rarely detected in clinic, and comprising ˜0.5% of all the B-NHL and BCP-ALL.

Kimiyoshi Sakaguchi et al. had conducted the literature survey to further shed light on the clinical and immunological features of pre-BLL compared to BCP-ALL[15]. Compared to his research, we failed to observe a relatively older median age (6.8y) and a higher UA level (6.93mg/dl) of our patients, but we could observe an elevated level of LDH (median >5,700 IU/l), which was consistent with other researches. The blast immunophenotypes reported in other researches were similar to that of our patients.

With the improvement in standard chemotherapy and supportive care, the outcome for pediatric BL and BCP-ALL has improved with a 5-year overall survival (OS) rates achieve 90%[16, 17]. Despite with the immunophenotype of BCP-ALL and the genetic characteristic of BL, the biological characteristics and treatment of pre-BLL are still controversial. By using next generation sequencing (NGS), Wagener et al. have uncovered that pre-BLL shows similar molecular features of BCP-ALL rather than BL, with recurrent NRAS/KRAS mutations, lack of functional B-cell receptor and c-MYC translocation due to aberrant VDJ recombination, instead of class switch or somatic hypermutation like mature B-cell neoplasms[18, 19]. Whereas protocols for BL consist of short-course and high-intensity pulsed chemotherapeutic regimen, protocols for BCP-ALL are characterized by continuous treatment regimen with a long-term maintenance therapy of low intensity. Based on the literature survey and several cases, Herbrueggen et al. encouraged treatment of pre-BLL according to protocols for mature B-cell NHL rather than BCP-ALL[3]. In this study, five patients were treated with mature B-cell neoplasm protocols and one (1/5) relapsed in a short time (5 months). Among the other four patients who was treated with BCP-ALL protocols, two (2/4) relapsed before termination of treatment. It is suggested that the outcomes of pre-BLL patients appear to be favorable when treated with protocols used for mature B-cell neoplasm. Sakaguchi et al. have suggested that high-risk ALL-type treatment might be adequate for the treatment of pre-BLL[15,] but there is still inconclusive how intensive the chemotherapy should be.

Although with a molecular similarity to BCP-ALL, the presence of the c-MYC warrants intensive treatment due to the highly proliferate nature of pre-BLL. However, the intensity of chemotherapy, the value of the supplemented of targeted drug like rituximab and the necessity of maintenance therapy are still unknown. Some patients relapsed even when treated with high-intensity regimen, suggesting further genetic studies should be performed. In view of the rarity of pre-BLL, international collaborative efforts are encouraged to further elucidate the biological and clinical characteristics of pre-BLL and finally establish a consensual treatment approach.

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CONFLICTS OF INTEREST

There are no competing financial interests.

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