Clinical Research

Significance of myeloid antigen expression in precursor T lymphoblastic lymphoma

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Abstract

Background and Objective: Precursor T lymphoblastic lymphoma (T-LBL) is a highly aggressive lymphoma. Myeloid antigen expression was found in some of the patients, and its clinical significance is worth studying. This study was to compare the clinical features, short-term efficacy and survival of T-LBL patients with or without myeloid antigen expression so as to evaluate its prognostic significance.

Methods: Forty-five T-LBL patients, with a median age of 14 years, were treated at Sun Yat-sen University Cancer Center between January 2000 and July 2008. These patients were divided into myeloid antigen-positive group (My(+) group) and myeloid antigen-negative group (My(−) group) based on the flow cytometric (FCM) analysis in bone marrow or pleural fluid. Myeloid antigen expression and its correlation with the short-term efficacy and overall survival were assessed in the two groups.

Results: There were 18 patients (40.0%) in the My (+) group and 27 (60.0%) in the My (−) group. The myeloid antigen expression was negatively correlated with the initial level of lactate dehydrogenase (LDH), but not with other clinical features. The remission rate was lower in the My(+) group than in the My(−) group (38.8% vs. 70.3%, \(P = 0.028\)). The 2-year overall survival rate was lower in the My (+) group than in the My (−) group (51.9% vs. 78.7%, \(P = 0.036\)). By age subgroup analysis, there were no differences in response and survival rate among children and adolescents with or without myeloid antigen expression. But the remission rate and the 2-year overall survival rate were significantly lower in adult patients with myeloid antigen expression than in patients without it. Univariate and multivariate analysis demonstrated that age and myeloid antigen expression were adverse prognostic factors.

Conclusion: Myeloid antigen expression is a predictor of a poor response to chemotherapy, and adverse prognostic factor in adult T-LBL, but not in children with T-LBL.

Key words: Lymphoma, myeloid antigen, flow cytometry, efficacy, prognosis

Precursor T lymphoblastic lymphoma (T-LBL) is a highly aggressive lymphoma. While lymphatic antigen expression is the major immuno-phenotype, quite a few patients present mixed series expression (such as myeloid antigen). Currently, there are numerous studies on the association of myeloid antigen expression with clinical features and outcomes in acute lymphoblastic leukemia (ALL), yet the results are conflicting. In the 1990s, most investigators thought that ALL patients with myeloid antigen expressions were expected to have a poor prognosis, especially in adults. But in recent years, it was found in many studies that myeloid antigen expression in ALL was not correlated with clinical outcomes. Lymphoblastic lymphoma and acute leukemia are the same entity with different clinical features, and reports of lymphoblastic lymphoma with myeloid antigen expressions are rare. Our study was aimed to describe the features of myeloid antigen expressions in T-LBL patients, and analyze their associations with biological characteristics, short-term therapeutic efficacy and prognosis.

Materials and Methods

Clinical data

Clinical data and bone marrow (or pleural effusions) of 45 T-LBL patients treated at Sun Yat-sen University Cancer Center between August 2000 and August 2008 were collected. Diagnosis was established through pathological and bone marrow examinations. There were 31 males and 14 females with a median age of 14 years (range: 5.5–66 years). Twenty-eight patients were first diagnosed under the age of 18. Judged by St
Jude staging system, there were seven cases of stage III and 21 of stage IV T-LBL. And 17 patients were first diagnosed above the age of 18, all were stage IV by Ann/Arbor staging system. Other clinical characteristics are shown in Table 1. Bone marrow involvement was defined if the proportion of blasts arranged between 5%–25%.

**Immunophenotypic analysis**

Bone marrow of 41 patients and pleural effusions of four patients before treatment were anticoagulated with heparin and preserved in 4°C refrigerator, and analyzed within 48 h. The used monoclonal antibody lymphatic lineage included cd5, cd3, cd5, cd7, cd10, cd19 and cd20; myeloid lineage included cd13, cd14, cd15, cd33 and mpo; stem / hematopoietic lineage included td-t and cd34. Labeling was performed by routine FCM surface antigen and intracellular antigen. The software CellQuest was used for analysis. Percentages of each cell groups were calculated by CD45/SSC method to distinguish between tumor cells and normal mature cells. Then tumor cells were analyzed using five parameters of FSC, SSC, McAb1-FITC, McAb2-PE and CD45-CyChrom to determine their immunophenotype. Criteria for My+ group with combined myeloid antigen expression were: tumor cells expressed any one of myeloid antigens (CD13, CD14, CD15, CD33 and MPO) besides lymphatic antigens. My (-) group exclusively expressed lymphatic antigens.

**Treatment strategies**

Of the 45 patients, 38 received only chemotherapy, five were treated with chemotherapy and whole brain radiotherapy, and two patients were treated with chemotherapy and autologous stem cell transplantation. Patients under 18 years of age were subjected to T-NHL-BFM-90 regimen and those older than 18 to high intensity regimens such as EPOCH, HyperCAVD, and combined chemotherapy using prophylactic intrathecal injection. One child failed in the induction therapy because of disease progression.

**Follow-up**

Follow-up was conducted until June 1, 2009 by medical history tracing, telephone contact and written correspondences.

**Evaluation of therapeutic efficacy**

For the patients treated with BFM-90 regimen, short-term efficacy was evaluated after induction chemotherapy (Ia+Ib), for those treated with EPOCH or other regimens, short-term efficacy was evaluated after two treatment cycles. Efficacies were evaluated according to the revised version of International Malignant Lymphoma Evaluation Criteria: complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), response rate (RR) = CR + PR, no response (NR) = SD + PD.

**Statistical analysis**

SPSS16.0 software was used for analysis. Myeloid antigen expression of patients with different clinicopathologic characteristics were compared using Chi-square test. Efficacy was evaluated based on the survival data by Kaplan-Meier method. Log-rank was used for the univariate analysis and Cox model was used for multivariate analysis. Significant difference was defined when $P < 0.05$.

**Results**

**Myeloid antigen expressions in T-LBL**

Of the 45 patients, all expressed CyCD3 and CD7, 37 (82.2%) expressed TdT, 35 (77.8%) expressed CD5, 24 (53.3%) expressed cd3 and 19 (42.2%) expressed CD34; 18 (40.0%) had concomitant myeloid antigen expression, including 12 (26.7%) expressing CD13, nine (20.0%) expressing CD33, and three (6.7%) expressing both CD13 and CD33. CD34 was expressed at a higher level in My (+) group than those in My(-) group (66.7% vs. 25.9%, $P = 0.0007$).

**Relationship between myeloid antigen expression and clinical characteristics of T-LBL**

Myeloid antigen expression was correlated with the LDH levels of patients with T-LBL in the initial evaluation ($P < 0.05$). Patients with LDH < 500 U/L showed high myeloid antigen expression. Myeloid antigen expression did not correlate with gender, age, mediastinal mass, large mass, number of extranodal lesions, B symptoms, PS score, count of leukocyte and platelet, bone marrow blast proportion ($P > 0.05$) (Table 1).

**Influence of myeloid antigen expression on short-term efficacy and survival rate of T-LBL patients**

The patients were followed-up till June 1, 2009 with a median period of 27 months (7–110 months). Fourteen patients died, 29 were still under follow-up and two were lost to follow-up. Treatment efficacy was evaluable in 45 patients. The CR rate of My (-) group was significantly lower than that of My (+) group (38.8% vs. 70.3%; $P = 0.028$); ORR of My (+) group was lower than that of My(-) group (83.3% vs. 96.2%; $P = 0.136$). The 2-year overall survival rate of the whole group was 68.4%, and the survival rate of My (-) group was significantly higher than that of My(+) group (78.7% vs. 51.9%; $P = 0.036$; Figure 1).

**Influence of myeloid antigen expression on short-term efficacy and survival rate of T-LBL patients in different age subgroups**

Of the 45 patients, 28 were under 18 years old and 17 were more than 18 years old. Among the patients of under 18 years old, the CR rate of My(+) and My(-) groups were similar (87.5% vs. 95.0%, $P = 0.746$), and the 2-year survival rates were not significantly different (75.0% vs. 86.1%; $P = 0.484$, Figure 2). Among the patients of more than 18 years old, the CR rate was significantly higher in My(-) group than in My(+) group (42.9% vs. 10.0%; $P = 0.043$), so was the 2-year survival rate (62.5% vs. 27.8%; $P = 0.047$, Figure 3).

**Influence of myeloid antigen expression and clinical characteristics on survival rate of T-LBL patients**

Univariate analyses showed that gender ($P = 0.096$), stage ($P = 0.613$), PS score ($P = 0.596$), mediastinal mass ($P = 0.412$), giant mass ($P = 0.097$), initial level of LDH ($P = 0.521$), white blood cell count ($P = 0.232$), platelet count ($P = 0.907$) and CD34 ($P = 0.772$) were not associated with the prognosis, while positive myeloid antigen expression ($P = 0.036$) and age ($P < 0.001$)
Figure 1  Survival curves of T lymphoblastic lymphoma (T­LBL) patients with or without myeloid antigen expression were prognostic risk factors.

Factors of $P \leq 0.1$ in univariate analysis were introduced into Cox multivariate analysis, showing that age ($P < 0.001$) and positive myeloid antigen expression ($P = 0.024$) were independent prognostic risk factors.

Discussion

T-LBL is a highly invasive and progressive lymphatic malignant tumor. LBL accounts for 25%–30% of non-Hodgkin's
lymphoma (NHL) in children and 2% in adults\cite{8}. The effects of myeloid antigen expression on clinical characteristics and prognosis of T-LBL were debated in previous studies. The biological activity of LBL is similar to that of acute lymphatic leukemia (ALL), and WHO lymphoma classification system (2000) classified LBL and ALL into the same type (T-LBL/ALL). Lymphatic antigen expression is the primary immunophenotype of LBL, while some LBL may present mixed series expressions such as concomitant myeloid antigen expression. It is reported that myeloid antigen expression accounts for 10%–43% of the ALL, without significant differences between B-ALL and T-ALL\cite{9}. Chang et al.\cite{10} reported that positive CD33 was found most frequently with a positive rate of 15.7%, accounting for 72.7% of My(+) cases; while other studies\cite{4,6} showed that CD13 was most common with a positive rate of 13.0%–17.4%, accounting for 69.4%–80.5% of My(+) cases. In our study, 40.0% of T-LBL had concomitant myeloid antigen expression, which was consistent with other studies. Myeloid antigens were predominantly CD13 and CD33, without significant difference (P > 0.05).

Most studies showed that myeloid antigen expression was not associated with clinical characteristics when first diagnosed\cite{4,6}. Xicoy et al.\cite{8} reported that myeloid antigen expression of T-ALL was not significantly associated with its clinical characteristics and biological activities. Preti et al.\cite{7} found that myeloid antigen positive ALL was typically characterized by increased ALP level, thrombocytopenia, leukocytosis and older age. T-LBL is manifested by mediastinal mass, lymphadenopathy and involvement of bone marrow and central nervous system (CNS). The present study showed that myeloid antigen expression was not associated with gender, age, mediastinal mass, large mass, number of extranodular lesions, B symptoms, PS scores, count of leukocyte and platelet, bone marrow blasts proportions (P > 0.05), but high levels of LDH in My (+) group were seen less frequently than in My(−) group.

In recent years, treatment of adolescent LBL with intensive regimens similar to that for ALL has achieved favorable outcomes with a five-year event-free survival (EFS) of 70%–90%\cite{11}. Adult LBL was treated with intensive chemotherapy regimens such as HyperCVAD and EPOCH, achieving a short-term CR of 70%–85%\cite{12}. However, the five-year survival rate of high-risk children and LBL adult was lower than 50%, and maintenance of remission was short\cite{13}. The key issue of improving LBL outcome is how to determine high-risk patients to initiate appropriate treatment. Presently, there were numerous studies focusing on the relationship between myeloid antigen expression and ALL outcomes, while its association with LBL is rarely investigated. Because of the disparities of myeloid antigen expression criteria, treatment regimens and timing of efficacy evaluations, the results are difficult to interpret. Most investigators found that myeloid antigen expression did not influence the early CR rate, persistent remission time and prognosis of ALL patients\cite{14–16}. Vitale et al.\cite{11} reported that myeloid antigen expression was not correlated with remission rate and remission duration of ALL. Drexler et al.\cite{17} found that myeloid antigen expression could influence the early remission rate and progression-free survival (PFS) in adult ALL, while this has never been tested in children. Pituch et al.\cite{18} reported that myeloid antigen expression in children's ALL was correlated with multidrug resistance molecule (MDR) and CD34 expression rate, and MDR expression could inhibit in vitro apoptosis of lymphocytes indirectly. The remission duration of My (+) ALL was significantly longer than those of My (-). The present study found that the early remission rate of My (+) patients was significantly lower than My (-) patients (P = 0.028). Further subgroup analysis indicated that positive myeloid antigen expression did not influence early remission rate in children (87.5% vs. 95.0%; P = 0.746); while early remission rate of adult patients was significantly lower in My (+) group than in My(-) group (10.0% vs. 42.9%; P = 0.043), which was consistent with some previous studies\cite{19}. Our results suggest that early remission is difficult to achieve in adult patients with positive myeloid antigen expression, while we didn't observe the same results in the children.

The 5-year survival rate and relapse rate after remission of My (+) ALL were not significantly different from My (-) ALL\cite{16–18}. The total and disease-free survival rates were not affected by myeloid antigen expression in children with ALL in the study of Unal et al.\cite{20}. However, My (+) patients were more likely to be categorized into high risk group and received more intense regimens. Yanenel et al.\cite{21} suggested that myeloid expression in adult may result in better long-term survival. Drexler et al.\cite{17} found that myeloid antigen expression was not a prognostic factor in children with lymphatic leukemia, but a prognostic risk factor in adult. Follow-up duration of our study was short (27 months) and only the 2-year survival was analyzed. The 2-year survival rate of My (-) group was significantly higher than that of MY (+) group (78.7% vs. 51.9%; P = 0.036), indicating the importance of myeloid antigen expression. Further analysis of subgroups classified by age showed that the 2-year total survival rate of children was not influenced by myeloid expression (75.0% vs. 86.1%; P = 0.484), but the 2-year survival rate of My (+) group was significantly lower than that of adult My(-) group (P = 0.047). Univariate analysis showed that myeloid expression (P = 0.036) and age (P = 0.001) were prognostic risk factors of T-LBL, and gender, stage, large mass, mediastinal mass and CD34 expression were not associated with the prognosis. Multivariate analysis showed that myeloid expression and age were
independent prognostic risk factors of T-LBL \( (P = 0.002, 0.024) \), which do not include gender. \( (P > 0.05) \). Results of our study suggest that the survival rate of adult T-LBL with myeloid expression is significantly lower than those with negative myeloid expression, while this phenomenon is not observed in children probably because these children have received high intense chemotherapy regimens as adopted in ALL\(^1\). However, the adult sample was small in this study and treatment regimens were different, which remarkably compromised the statistical power. And further investigations with larger sample size are needed.

In conclusion, our study suggests that the survival rate of adult T-LBL patients with myeloid expression is significantly lower than those with negative myeloid expression, while this phenomenon is not observed in the children.

References