The prognostic impact of myeloid antigen expression in pediatric acute lymphoblastic leukemia patients

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The incidence of mixed-lineage leukemias in the pediatric age group was previously reported as 13.8% for myeloid antigen-positive ALL and 11.1% for lymphoid antigen-positive acute myeloid leukemia (AML). Recent studies showed that extensive chemotherapy protocols overcome the risk of myeloid lineage. Our study also supports most of the previous data and we postulate that myeloid antigen expression in pediatric ALL cases has insignificant effect on clinical presentation, relapse rates and survival. Importantly, 54% of myeloid antigen-expressing ALL patients received high-risk treatment protocols for some other reasons and this may also have contributed to similar outcome in these patients to that observed in myeloid antigen-negative ALL patients.

Key words: myeloid, acute lymphoblastic leukemia, pediatric, prognosis.

The outcome for children with acute lymphoblastic leukemia (ALL) has improved dramatically with current therapeutic strategies resulting in an event-free survival (EFS) exceeding 75% for most patients. However, significant challenges remain, including developing better methods to predict which patients can be cured with less toxic treatment and which will benefit from augmented therapy. In addition, 25% of patients fail therapy and novel treatments that are focused on undermining specifically the leukemic process are needed urgently[1]. In the categorization of risks in childhood ALL, clinical factors (white blood cell [WBC], age and rate of response to therapy) are combined with identification of cytogenetic and molecular genetic abnormalities, and most recently with the monitoring of the minimal residual disease by molecular methods[2-8]. Immunophenotyping by flow cytometry aids in distinguishing ALL from acute myeloid leukemia (AML) in approximately 10% to 15% of cases in which morphology and cytochemistry are inadequate to make a definitive diagnosis[9]. The incidence of mixed-lineage leukemias in the pediatric age group was previously reported as 13.8% for myeloid antigen-positive ALL and 11.1% for lymphoid antigen-positive AML[10]. Recent studies showed that extensive chemotherapy protocols overcome the risk of myeloid lineage. In this retrospective study, we aimed to investigate whether the myeloid antigen positivity at the time of diagnosis in immunophenotyping by flow cytometric analysis has a prognostic impact on the relapse and survival rates in the follow-up in pediatric ALL cases, in whom we used St. Jude Total XI and XIII ALL protocols with minor modifications.

Material and Methods

A total of 197 children and adolescents up to 16 years of age at the time of diagnosis between March 1991 and July 2003, with newly diagnosed ALL in the Division of Pediatric Hematology, Hacettepe University Faculty of Medicine were analyzed retrospectively. Twenty-nine patients with unavailable immunophenotyping and four patients who were lost during remission induction treatment were excluded from the study, and the analyses were made over 164 patients. The diagnosis of ALL was based on morphological, cytochemical, immunophenotypic (by flow cytometric analysis, FACScan; Becton Dickinson, San Jose, CA, USA), cytogenetic and molecular

genetic analysis of bone marrow aspirates. CD2, CD5, CD7, CD13, CD14, CD33, CD10, CD19, CD20, CD22, CD34, CD117 and HLA-DR panel of monoclonal antibodies was used for immunophenotyping. Antigen positivity was determined by flow cytometry on a FACScan with a cut-off value of 20%. Central nervous system (CNS) involvement was determined by cytologic and biochemical evaluation of the cerebrospinal fluid (CSF), whereas skeletal and mediastinal involvements were detected by plain radiographic evaluations. Patients received St. Jude Total XI study protocol with minor modification[8] between March 1991 and March 1997. Between March 1997 and July 2003, they were given slightly modified St. Jude Total XIII study protocol[11].

Patients were grouped into five according to immunophenotypes at presentation: Group 1 with one myeloid antigen-positivity (n=23, 14%), Group 2 with two myeloid antigen-positivity (n=10, 6.1%), Group 3 with T-cell and B-cell markers expression (biphenotypic ALL) (n=16, 9.8%), Group 4 with B-cell markers expression (n=91, 55.5%), and lastly Group 5 with T-cell markers expression (n=24, 14.6%). One or two myeloid antigen-positive groups were also combined as Group A (n=33, 20%), and the rest as Group B (n=131, 80%).

Statistical analyses were performed by SPSS version 11, Chicago, IL, USA. Overall survival (OS) was estimated from the date of diagnosis until the date of death. EFS was defined as time in first complete remission, until death or relapse. OS and EFS were estimated by Kaplan-Meier analysis, using the log rank test for comparisons. Differences in the distribution of variables among patient groups were analyzed using chi-square, ANOVA and Kruskal-Wallis tests. A p-value <0.05 was regarded as statistically significant.

Results

The characteristics of the 164 patients who were included in the study are shown in Table I. Of the 164 patients, 68.3% were male and the median age at diagnosis was 72 months (range 4-192). The gender and ages of groups were similar ($p>0.05$). There was no statistically significant difference between groups in terms of hemoglobin, WBC, thrombocyte count and CNS and mediastinal involvement at the time of diagnosis. Skeletal involvement was statistically more common in Group A.

Table I. Clinical and Laboratory Characteristics of Patients at Diagnosis

	Group1	Group 2	Group 3	Group 4	Group 5	Total
n	23	10	16	91	24	64
Median age (month)	60	54	72	72	108	72
Male/Female	14/9	8/2	12/4	64/27	14/10	112/52
Hemoglobin (g/dl)	7.7±2.5	7.3±2.4	7.0±2.9	7.9±2.4	8.3±2.9	7.8±2.6
WBC (%)						
$<5x10^9$/L	21.7	20	6.3	24.3	33.3	23.2
5-100x10^9/L	65.3	70	81.2	66.9	41.7	64.6
$>100x10^9$/L	13	10	12.5	8.8	25	12.2
Median thrombocyte (/μl)	60000	52500	50000	50000	50000	50000
Median LDH (IU/L)	818	865	513	656	578	795
CNS infiltration	8.7	10	12.5	4.4	12.5	7.3
Mediastinal involvement	–	–	18.8	3.3	29.2	7.9
Treatment risk group						
High risk	61	40	73	61	79	64
Intermediate risk	13	10	20	14	8	13
Low risk	26	50	7	24	12	23
5-year event-free survival (%) (p=0.89)	74±10	86±13	76±1	66±6	71±11	74±7
5-year overall survival (%) (p=0.65)	73±10	100±0	93±7	77±5	66±10	81±6
Relapse rate (%)	26	20	19	32	25	28

WBC: White blood cell. LDH: Lactate dehydrogenase. CNS: Central nervous system.

Of 164 patients, in the five groups, 61%, 40%, 73%, 61% and 79% received high-risk treatment protocols, respectively, and there was no difference in terms of risk groups between the five groups. While 54% of Group A and 66% of Group B received high-risk treatment protocols, the difference was insignificant (p=0.27). Relapse rates were 26%, 20%, 19%, 32% and 25% in Groups 1 to 5, respectively, and the difference was insignificant (p=0.6). Relapse rates were also statistically similar between Groups A and B (24% versus 29%).

Five-year EFS and five-year OS of Groups 1 to 5 were statistically similar (p=0.89 and p=0.65, respectively) (Table I). Similarly, of Groups A and B, five-year EFS (Group A: 78±8%, Group B: 68±5%) and five-year OS (Group A: 81±8%, Group B: 77±4%) were statistically similar (p=0.60 and p=0.67, respectively). Five-year EFS and five-year OS of Groups 1 and 2 were also similar (p=0.91 and p=0.44, respectively). Although the sample sizes were small, we made an analysis within Group A patients in terms of treatment protocol risk groups and found no difference in EFS and OS of the myeloid antigen-positive group who received low-, intermediate- or high-risk treatment protocols (data not shown).

Discussion

Immunophenotyping has become essential in the diagnosis of acute leukemia, allowing not only the differentiation level of the clone and the presence of aberrant markers, but also detection of minimal residual disease in acute leukemia[12]. Cases with aberrant patterns of marker expression, so-called acute mixed lineage leukemia, are frequently encountered in both ALL and AML, and can lead to diagnostic confusion. However, correlation with morphology and other clinicopathologic features and careful consideration of the weight of phenotyping evidence almost always allows the correct lineage to be identified[13]. In childhood ALL, myeloid antigen expression was reported as high as 21.2%, with CD13 and CD33 expressions being more common[14].

The prognostic value of phenotypic information in acute leukemia is generally limited and the prognostic importance of myeloid antigen expression in childhood ALL is controversial. Although mixed lineage positivity was considered as a poor prognostic factor previously, this has been overcome recently with the intensification of leukemia protocols. In the Children's Cancer Group, St. Jude study and reports from Italy, myeloid antigen expression in childhood ALL was not reported as an adverse prognostic factor[15-17]. However, in a study from Japan, myeloid antigen expression in ALL was found as an unfavorable prognostic factor[18]. In the study from China, there was no significant difference in clinical and biological features and chromosome abnormality between myeloid antigen-positive and myeloid antigen-negative cases and additionally, there was no significant difference in complete remission and relapse rates between the two groups[14].

Our study also supports most of the previous data. We postulate that myeloid antigen expression in pediatric ALL cases has an insignificant effect on clinical presentation, relapse rates and survival. Importantly, 54% of myeloid antigen-expressing ALL patients received high-risk treatment protocols for some other reasons, and this may also have contributed to similar outcome in these patients to that observed in myeloid antigen-negative ALL patients.

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