Brief report

Prognostic significance of CD20 expression in childhood B-cell precursor acute lymphoblastic leukemia

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CD20 expression is associated with inferior survival in adults with acute lymphoblastic leukemia (ALL). We analyzed the prognostic impact of CD20 expression in 353 children with B-cell precursor ALL treated in 3 consecutive St Jude Total Therapy studies. CD20 expression (> 20%) was found in 169 patients (48%) and was more frequent in patients between 1 and 10 years of age than in those younger than 1 or older than 10 years ($P = .001$). None of 14 patients with *MLL-AF4* expressed CD20. There was no association between CD20 expression and *E2A-PBX*, *TEL-AML1*, ploidy, white blood cell count at diagnosis, or sex. In contrast to the experience in adult ALL, our patients with CD20 expression tended to have a better treatment outcome than those without the expression: 5-year event-free survival 84% ± 2.9% versus 78% ± 3.1% ($P = .08$). These data suggest that CD20 expression is not associated with inferior outcome in pediatric patients treated with contemporary regimens. (Blood. 2006;108:3302-3304)

Introduction

As intensification of acute lymphoblastic leukemia (ALL) chemotherapy is reaching a limit, targeted therapy may further improve treatment outcome by increasing the efficacy and decreasing the toxicity of standard regimens. In an effort to improve the outcome of adult ALL, a disease with a 60% failure rate, investigators are exploring the benefits of combining targeted therapy to standard chemotherapy regimens. Incorporating imatinib mesylate, an inhibitor of the *BCR-ABL* tyrosine kinase, into the hyper-Cytoxan (cyclophosphamide), vincristine, Adriamycin (doxorubicin), dexamethasone (hyper-CVAD) regimen for adult ALL with t(9;22) has improved the outcome of this population compared to that of patients previously treated with hyper-CVAD alone.[1] Imatinib has now also been integrated into treatment regimens for pediatric Philadelphia chromosome–positive ALL.

Rituximab is a chimeric monoclonal antibody to CD20 that is expressed on normal and malignant B lymphocytes. Favorable experience has been reported for the use of rituximab in combination with chemotherapy in mature B-cell lymphoma and leukemia.[2,3] Because CD20 expression was associated with poor prognosis in adult ALL, the M. D. Anderson Cancer Center (Houston, TX) group incorporated rituximab in the treatment regimens for adults with B-cell precursor ALL. In the Anderson Cancer Center study in which the hyper-CVAD regimen was modified to incorporate rituximab for patients expressing CD20, the 1-year disease-free survival rate was 100% for $CD20^+$ (compared to 49% for similar patients treated on the original hyper-CVAD regimen, $P = .03$) and 61% for $CD20^-$ patients.[4] Follow-up at 2 years disclosed a disease-free survival rate of 73% for the 27 patients with $CD20^+$ ALL treated with rituximab compared to 40% for the 36 patients with $CD20^-$ ALL ($P = .04$).[5]

To determine the prognostic impact of CD20 expression in pediatric patients with B-cell precursor ALL and the potential utility of rituximab in this subset of patients, we studied 353 children with B-cell precursor ALL treated at St Jude Children's Research Hospital.

Study design

The cohort consists of 353 patients with B-cell precursor ALL treated on St Jude protocols Total 13A,[6] Total 13B,[7] and Total 14[8] between December 1991 and May 1999. CD20 positivity was defined as expression of CD20 in more than 20% of leukemia blasts. Immunophenotyping and cytogenetic and molecular genetic analyses were performed with methods as previously reported.[7] Survival and event-free survival were analyzed using the Kaplan-Meier method[9] with the associated standard errors calculated using the method of Peto et al.[10] Survival comparisons were done by the Mantel-Haenszel test.[11] Cumulative incidences of any relapse observed in the cohort were analyzed using the Gray estimator with incorporation of second malignancies and death in remission as competing risks.[12] The χ^2 tests were used to test association among categorical variables. Approval for these studies was obtained from the St. Jude Children's Research Hospital Institutional Review Board. All patients signed Institutional Review Board informed consent statements as per institutional policy and federal law requirements, and in accordance with the Declaration of Helsinki.

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Results and discussion

Of 353 children with B-cell precursor ALL, 169 (48%) expressed CD20 (> 20%). As shown in Table 1, children between 1 and 10 years were more likely to express CD20 as compared to infants younger than 1 year of age or patients older than 10 years ($P = .001$). African American patients were more likely to express CD20 as compared to white patients or other ethnic groups ($P = .02$). None of 14 patients with *MLL-AF4* expressed CD20 ($P < .001$). The expression was detected in 71% of the 14 patients with *BCR-ABL* rearrangement and 47% of the 159 patients lacking *BCR-ABL* ($P = .07$). A higher frequency of CD20 expression was noted in patients with livers 5 cm or larger ($P = .001$) and those with spleens 5 cm or larger ($P = .02$) compared to patients with livers and spleens smaller than 5 cm. There was no association between CD20 expression and sex, white blood cell count at diagnosis, *E2A-PBX*, *TEL-AML1*, or ploidy.

Table 1. Presenting features and treatment failure according to CD20 expression

Presenting feature	CD20⁻, no. (%)	CD20⁺, no. (%)	*P*
Age, y			.001
Younger than 1	14 (93)	1 (7)	
1-10	121 (48)	131 (52)	
Older than 10	49 (57)	37 (43)	
WBC count, ×10⁹/L			.85
Less than 50	142 (52)	129 (48)	
50 or greater	42 (51)	40 (49)	
Sex			.33
Male	101 (55)	84 (45)	
Female	83 (49)	85 (51)	
Race			.02
White	150 (55)	122 (45)	
African American	17 (34)	33 (66)	
Other	17 (55)	14 (45)	
Liver size			.001
5 cm or larger	35 (38)	58 (62)	
Less than 5 cm	149 (57)	111 (43)	
Spleen size			.02
5 cm or larger	38 (42)	53 (58)	
Less than 5 cm	146 (56)	116 (44)	
DNA index			.07
1.16 or greater	36 (43)	47 (57)	
Less than 1.16	148 (55)	122 (45)	
Ploidy subgroup			.58‡
Diploid	25 (60)	17 (40)	
Hypodiploid	9 (39)	14 (61)	
Pseudodiploid	63 (53)	56 (47)	
Hyper 47-50	29 (51)	28 (49)	
Hyper over 51	49 (49)	51 (51)	
NA	9 (75)	3 (25)	
MLL-AF4			< .001
MLL-AF4⁺	14 (100)	0 (0)	
MLL-AF4⁻	170 (50)	169 (50)	
BCR-ABL			.07
BCR-ABL⁺	4 (29)	10 (71)	
BCR-ABL⁻	180 (53)	159 (47)	
E2A-PBX			.67
E2A-PBX⁺	9 (47)	10 (53)	
E2A-PBX⁻	175 (52)	159 (48)	
TEL-AML1			.66‡
TEL-AML1⁺	48 (57)	36 (43)	
TEL-AML1⁻	113 (54)	95 (46)	
TEL-AML1 NA	23 (38)	38 (62)	
Treatment failure*	34 (64)	19 (37)	.05
Induction failure	5 (71)	2 (29)	
Isolated BM relapse	21 (68)	10 (32)	
Other†	8 (53)	7 (47)	

For CD20⁻, n = 184; for CD20⁺, n = 169. BM indicates bone marrow; NA, not available.

*Includes induction failure due to refractory leukemia and relapse.

†Includes combined BM, isolated central nervous system (CNS), and combined CNS relapse.

‡Patients with missing values were excluded from analysis.

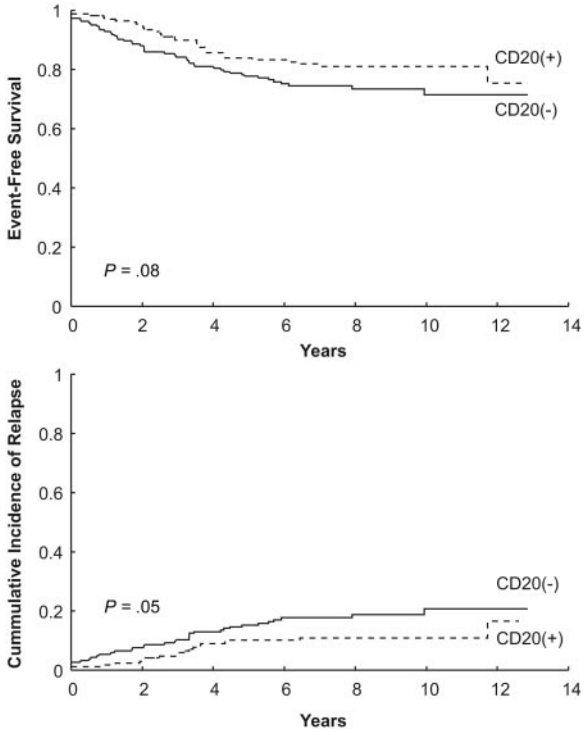

Figure 1. Event-free survival and risk of relapse according to CD20 expression.

In contrast to the experience in adult ALL, our patients with CD20 expression tended to have a better outcome than those without the expression (Figure 1): 5-year event-free survival 84% ± 2.9% versus 78% ± 3.1% ($P = .08$) and; 5-year overall survival 88% ± 2.5% versus 83% ± 2.8% ($P = .13$). In a multivariate analysis adjusting for the effect of other prognostic factors, CD20 expression was not an independent prognostic factor for overall survival ($P = .27$) or event-free survival ($P = .16$). However, patients with CD20 expression appeared less likely to have induction failure due to refractory leukemia or relapse ($P = .05$), as shown in Table 1 and Figure 1. When the 15 infants were excluded from our analysis, the CD20⁺ group still tended to have better event-free survival ($P = .3$) and lower relapse rate ($P = .1$).

Our results contrast with those reported by the Pediatric Oncology Group (POG). Among the 1231 patients 1 to 21.9 years old with newly diagnosed B-precursor ALL enrolled in POG studies between January 1991 and January 1994, CD20 expression (based on either a cutoff of 20% positivity on flow cytometry or fluorescence intensity) was associated with an inferior treatment outcome.[13] The discrepancy between our results and the POG observations most likely reflects treatment effects. Conceivably, the more effective treatment protocols used at St Jude's have eliminated the prognostic impact of CD20

expression. In this regard, St Jude's protocols have eliminated the adverse prognosis of African American race,[14] which was associated with CD20 expression. Additional studies are needed to determine if CD20 expression has a prognostic impact on other contemporary clinical trials.

These data suggest that CD20 expression is not an adverse prognostic factor in children with ALL treated on the St Jude protocols. It remains to be determined whether modification of current regimens for pediatric ALL to incorporate CD20-targeted monoclonal therapy would result in a clinical benefit as reported in adult studies.

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