Adverse prognostic significance of CD20 expression in adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia

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ABSTRACT

The prognostic significance of CD20 expression in B-cell precursor acute lymphoblastic leukemia (BCP-ALL) has been mostly studied in children and yielded conflicting results. In 143 adults with Philadelphia chromosome-negative BCP-ALL treated in the multicentric GRAALL 2003 trial, CD20 positivity over 20% was observed in 32% of patients. While not influencing complete remission achievement, CD20 expression was associated with a higher cumulative incidence of relapse (CIR) at 42 months (P=0.04), independently of the ALL high-risk subset (P=0.025). Notably, the negative impact of CD20 expression on CIR was only observed in patients with a white blood cell count (WBC) over 30×10^9/L (P=0.006), while not in those with a lower WBC. In the former subgroup, this impact translated into lower event-free survival (15% *vs.* 59% at 42 months, P=0.003). CD20 expression thus appears to be associated with a worse outcome, which reinforces the interest of evaluating rituximab combined to chemotherapy in CD20-positive adult BCP-ALL. *ClinicalTrials.gov ID, NCT00222027.*

Key words: CD20, acute lymphoblastic leukemia, rituximab, prognosis.

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Introduction

After improvement in treatment outcome of adult acute lymphoblastic leukemia (ALL) in recent decades, brought notably by intensive chemotherapy and increased use of allogeneic HSCT, a period of relative stagnation has been more recently observed.[1,2] Besides imatinib and other kinase inhibitors in Philadelphia chromosome (Ph)-positive ALL, one of the most promising new approaches in Ph-negative ALL relies on targeted therapy with monoclonal antibodies (MoAbs).[3,4] Indeed, ALL blast cells express a variety of antigens which may serve as targets, such as CD19, CD20, CD22, CD33, and CD52. The use of rituximab, a chimeric MoAb to CD20, has led to significant improvement of the outcome in patients with B-cell non-Hodgkin's lymphoma and also recently in those with Burkitt's or Burkitt-like mature B-cell ALL.[5,6] In patients with B-cell precursor (BCP) ALL, only case reports have been published regarding the therapeutic effect of rituximab.[7-10] Importantly, while the majority of mature B-ALL blast cells express CD20, only 30-50% of BCP-ALL blast cells do so.[3,11] This inconstant expression raises the issue of the potential prognostic significance of CD20 expression in BCP-ALL patients, which has been mostly studied in pediatric series and yielded conflicting results. A recent study performed at St Jude's Children's Research Hospital has reported that CD20 expression tend-

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ed to be associated with better outcome,[12] while an earlier study by the Pediatric Oncology Group reported a negative impact on treatment outcome.[13]

Here, we aimed to determine the prognostic impact of CD20 expression in adults with Ph-negative BCP-ALL by studying 143 patients prospectively treated in the multicenter GRAALL-2003 trial, designed to offer a dose-intensive pediatric-like approach in adults aged 15-60 years old with Ph-negative ALL.[14]

Design and Methods

Study design

The GRAALL-2003 study was a risk-adapted prospective Phase II trial, conducted in 70 centers in France, Belgium, and Switzerland. Between November 2003 and November 2005, 225 consecutive patients entered the study.[14] Patients diagnosed with a Ph-positive leukemia entered another specific study.[15] The planned chemotherapy has been previously detailed.[14] Response criteria and risk classification are notified in the footnote of Table 1. The treatment was influenced by risk classification at two different stages: (i) poor early responders were offered early reinforcement of the induction course; (ii) patients aged 55 years old or under were eligible for allogeneic stem cell transplantation (SCT) in first CR if they had high-risk ALL and an identified matched related or 10/10 allelic-matched unrelated donor. In risk factor analysis, we also included the older age over 45 years as a covariate since it was previously identified as significantly influencing overall survival in the same cohort of patients.[14]

Immunophenotyping

Immunophenotyping was performed in each local center, according to the general recommendations from EGIL[11] and the European LeukemiaNet, i.e. in multiparameter flow cytometry with CD45 gating of the blast population. Typical panels included B-cell-, T-cell- and at least two (CD13, CD33) myeloid-lineage markers, as well as CD10, CD34 and DR. Data, expressed as percentages of positive cells, were collected on a specific page of the centralized electronic case report form. Central review of the CD20 scattergrams was performed by MCB, checking for the positivity of residual B cells and assessing fluorescence shifts. Hospital laboratories are equipped with Beckman Coulter or Becton Dickinson flow cytometers and use commercial anti-CD20, according to local equipment policies.

Statistics

Overall survival and event-free survival (EFS) were calculated from the date of prephase initiation. Events accounting for EFS were failure of CR induction, relapse, and death. Outcome was updated as of December 15, 2007. The median follow-up of surviving patients was 37 months. Failure time data except cumulative incidences were estimated by the Kaplan Meier method,[16] then compared by the log-rank test, with hazard ratio (HR) estimated by the Cox model.[17] Proportional hazards assumptions were graphically checked. By contrast, in estimating CIR (respectively cumulative incidence of death in first CR), we took into account deaths in first CR (respectively relapses) as competing risks using the cumulative incidence curves, then compared by the Gray test while the Fine and Gray model was used to estimate subdistribution hazard ratio.[18] Type 1 error was fixed at the 5% level. All tests were two-tailed. All calculations were per-

Table 1. Characteristics and outcome according to CD20 expression in 143 patients with Ph-negative BCP-ALL.

	CD20-neg ALL (n=97)	CD20-pos ALL* (n=46)	*P* value**
Baseline factors			
Median age, years (range)	36 (15-60)	33 (17-60)	0.39
Age > 45 years, n (%)	25 (26)	11 (24)	0.99
WBC, x10^9/L (range)	6.7 (0.7-348)	6.8 (1.2-343)	0.69
CNS+, n (%)	1 (1)	0 (0)	0.99
MLL-AF4+, n (%)	21 (22)	0 (0)	<.001
E2A-PBX+, n (%)	5 (5)	2 (4)	0.99
Low hypodiploidy and/or near triploidy	4/97	2/46	0.99
Response-related factors			
Corticoresistance, n (%)	14 (14)	11 (24)	0.17
Chemoresistance, n (%)	40/93 (43)	20/46 (43)	0.99
Cortico- and/or chemo-resistance, n (%)	45/93 (48)	25/46 (54)	0.59
CR rate, n (%)	89 (92)	41 (89)	0.76
Post-induction MRD, n (%) ≥10^{-2} (clonal Ig rearrangements)	12/52 (23)	5/26 (19)	0.47
High-risk ALL*, n (%)**	**71/97 (73)**	**30/46 (65)**	**0.33**

**CD20 positivity is defined as expression of CD20 in more than 20% of ALL blasts. **Binary variables were compared with the Fisher's exact test. The Mann-Whitney test was used for median comparisons. ***High-risk ALL was defined by at least one of the following baseline or response-related high-risk factor: WBC≥30x10^9/L, clinical and/or morphological central nervous system (CNS) involvement, t(4;11) and/or MLL-AF4 fusion transcript, t(1;19) and/or E2A-PBX1 fusion transcript, low hypodiploidy (30 to 39 chromosomes or DNA index <0.85) and/or near-triploidy (60 to 78 chromosomes or DNA index 1.30 to 1.61), corticoresistance and/or early chemoresistance, absence of complete remission (CR) achievement after the first induction course, and a high minimal residual disease (MRD) level ≥10^{-2} at CR. Corticosteroid resistance (CsR) was defined as a peripheral blood blast cell count higher than 1.0x10^9/L at the end of the 7-day corticosteroid prephase. Chemotherapy resistance (ChR) was defined as a bone marrow blast cell percentage higher than 5% at the end of the first week of chemotherapy. Patients with corticosteroid resistant (CsR) and/or chemotherapy resistant (ChR) ALL were defined as poor early responders. Hematologic CR was defined according to standard criteria.*

formed using the STATA/SE software, version 9.0 (Stata Corporation, College Station, TX, USA) and the R software, version 1.5.1 (The R Development Core Team, A Language and Environment Copyright, 2002).

Results and Discussion

CD20 expression is associated with a higher CIR

CD20 positivity, defined as expression of CD20 in more than 20% of leukemia blasts, was observed in 32% of 143 patients, with a median percentage of blasts expressing CD20 of 74% (range 23-98). CD20 expression did not correlate with HLA-DR, CD34, or the myeloid markers CD13 and/or CD33 expression (in 74%, 96% and 20% of the 143 patients, respectively). Even though none of the 21 patients with *MLL-AF4* fusion transcript ALL did express CD20, CD20 expression was not associated with any other baseline or response-related factor included in the GRAALL definition of high-risk ALL (Table 1).

Once CR was obtained (130 out of the 143 patients), CIR was clearly affected by the GRAALL risk classification (P=0.025 in univariate analysis, Figure 1A). In parallel, CIR tended to be affected by CD20 expression (42% [95% CI, 28-59] *vs.* 29% [95% CI, 20-40] at 42 months in CD20-positive and CD20-negative patients, respectively; P=0.10 in univariate analysis; Figure 1B). By analyzing the impact of both risk classification and CD20 expression in a multivariate analysis, also including the older age over 45 years as a covariate, we observed that both the high-risk subset and CD20 expression were independently associated with a higher CIR (HR=2.7 [95% CI, 1.2-6.1], P=0.019; and HR=1.9 [95% CI, 1.01-3.5], P=0.045, respectively).

However, CD20 expression did not significantly impact on EFS (47% [95% CI, 32-61] *vs.* 54% [95% CI, 43-63] at 42 months in CD20-positive and CD20-negative groups, respectively; P=0.39) or overall survival (55% [95% CI, 39-69] *vs.* 59% [95% CI, 48-69] at 42 months in CD20-positive and CD20-negative groups, respectively; P=0.65). This could be partly related to an excess of treatment-related mortality among patients with CD20-negative ALL, since cumulative incidence of death in first CR was higher than in patients with CD20-positive ALL (12% [95% CI, 7-21] *vs.* 5% [95% CI, 1-18], respectively; P=0.20). The allogeneic SCT rate was 39/89 (44%) and 8/41 (20%) in the CD20-negative and CD20-positive subgroups, respectively (P=0.01). However, only 4 patients with CD20-negative ALL and no patient with CD20$^+$ ALL died in CR from the SCT procedure. The difference in SCT rate might thus not explain the excess of treatment-related mortality in patients with CD20-negative ALL mentioned above. Furthermore, when repeating outcome comparisons while censoring SCT patients at transplant time, no differences in EFS or OS emerged between both CD20 subgroups (*data not shown*).

Lastly, since the difference in SCT rate between both subgroups might be related to donor availability, we repeated the multivariate analysis including CD20 classification, older age over 45 years, and also donor availability (n=51 out of 91 patients eligible for allogeneic SCT in CR1), which confirmed a tendency for a higher CIR in the CD20-positive subgroup (HR=1.9 [95% CI, 0.9-4.0], P=0.07).

Prognostic interaction between CD20 expression and WBC at diagnosis

We aimed to evaluate if this negative prognostic value of CD20 expression, independent of the GRAALL risk classification, remained significant when adjusted, one-by-one, to each of the most frequent factors of this risk classification (WBC≥30×10^9/L, MLL-AF4, and CsR and/or ChR, which were observed in 28%, 15%, and 50% of patients, respectively). The trend for a higher CIR in CD20-positive ALL patients persisted after adjustment on WBC (P=0.04, while P=0.008 for WBC), but not on MLL-AF4 and early response (P=0.21 and 0.11, respectively).

We thus focused our analysis on the interaction between CD20 expression and WBC at diagnosis, by comparing the impact of CD20 expression on CIR according to WBC. As shown in Figure 2A, the negative impact of CD20 expression was only observed in the population of patients with higher WBC (70% [95% CI, 42-93] *vs.* 24% [95% CI, 12-46] at 42 months; P=0.006),

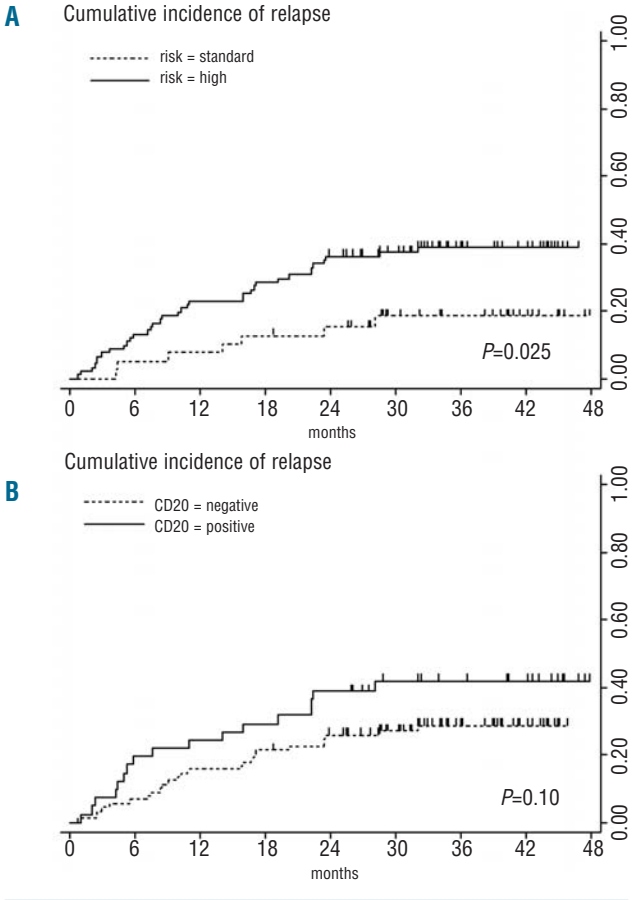

Figure 1. CIR according to (A) the ALL risk subsets and (B) CD20 expression. In 130 out of the 143 patients reaching first complete remission, CIR is influenced by the GRAALL risk classification and tends to be affected by CD20 expression.

but not in those with lower WBC (33% [95% CI, 19-53] *vs.* 31% [95% CI, 21-44] at 42 months; *P*=0.77). This negative impact of CD20 expression in the former patient subgroup also translated into shorter EFS (15% [95% CI, 2-39] *vs.* 59% [95% CI, 39-75] at 42 months; *P*=0.003), as shown in Figure 2B. In contrast, such effect was not found in patients with lower WBC (42-month EFS, 60% [95% CI, 41-74] *vs.* 51% [95% CI, 38-63]; *P*=0.45). Consequently, the negative impact of WBC at diagnosis was only observed in patients with CD20-positive ALL (*P*= 0.01 and 0.0003 for CIR and EFS, respectively) but not in those with CD20-negative ALL (*P*=0.67 and 0.66 for CIR and EFS, respectively). Again, this could not be explained by differences in post-remission therapy, *i.e.* allogeneic SCT. Actually, 7 out of the 10 CR patients with high WBC CD20-positive ALL (70%) had a donor, as compared to 16 out of the 25 CR patients with high WBC CD20-negative ALL (64%). Three patients were not transplanted in first CR in the former subgroup, all because of early relapse, while 2 patients were not transplanted in first CR in the latter subgroup, including only one early relapse. Furthermore, 3 out of 4 patients relapsed after SCT in the former subgroup, as compared to only 4 out of 14 patients in the latter subgroup. Relapse, therefore, remained a frequent event in those patients with high WBC CD20-positive ALL, despite the existence of a donor or even SCT.

Very recently, a similar association between CD20 expression and worse outcome has been reported in adults with BCP-ALL treated at the M.D. Anderson Cancer Center (MDACC).[19] In contrast to our study, this series included Ph-positive ALL patients (52 out of 253). The frequency of CD20 expression, defined with the same cut-off of 20% positive blast cells, was also higher than in our cohort (47% *vs.* 32%). After two different front-line chemotherapy regimens (conventional VAD/CVAD or intensive hyper-CVAD), CD20 positivity was also found to be associated with a worse outcome, *i.e.* lower 3-year rates of complete remission duration and overall survival. As in our cohort, the primary cause of failure was related to a higher incidence of systemic disease recurrence in the CD20-positive group, regardless of therapeutic regimen (68% *vs.* 33% for hyper-CVAD, *P*=0.02; 80% *vs.* 35% for VAD/CVAD, *P*=0.01). Interestingly, the adverse impact of CD20 expression was found to be most apparent in the youngest age group of patients (30 years or under). Overall, although the treatment differed in these two series, both confirm a pejorative impact of CD20 expression in adult BCP-ALL, more marked in younger patients in the MDACC study and in those with high WBC in the present one. Due to the relatively small patient numbers, further investigations are warranted to confirm and try to understand the peculiar negative impact of CD20 expression in patients with high

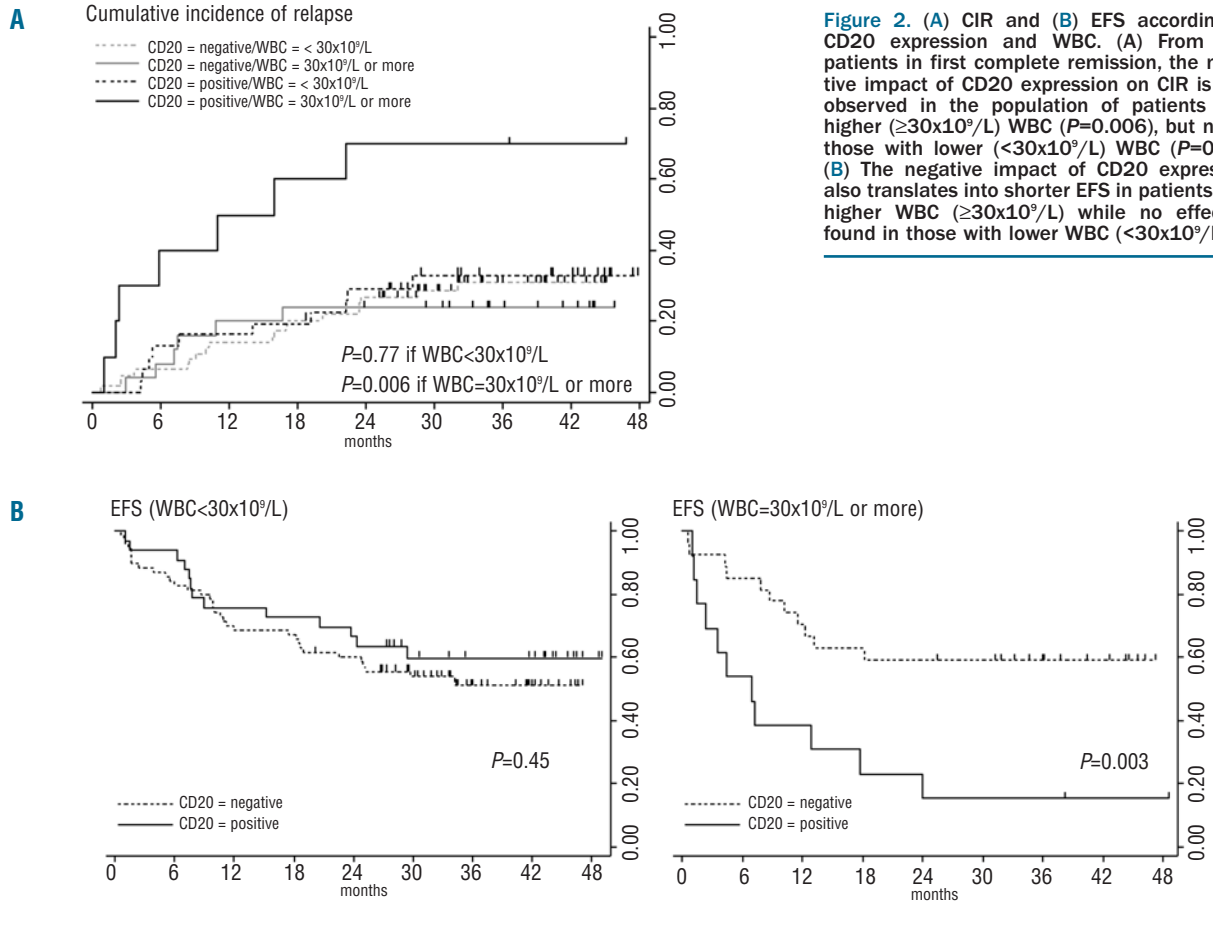

Figure 2. (**A**) **CIR and** (**B**) **EFS according to CD20 expression and WBC. (A) From 130 patients in first complete remission, the negative impact of CD20 expression on CIR is only observed in the population of patients with higher (≥30x10⁹/L) WBC (*P*=0.006), but not in those with lower (<30x10⁹/L) WBC (*P*=0.77). (B) The negative impact of CD20 expression also translates into shorter EFS in patients with higher WBC (≥30x10⁹/L) while no effect is found in those with lower WBC (<30x10⁹/L).**

WBC ALL. Interestingly, another recent finding was an upregulation of CD20 expression during induction treatment of pediatric BCP-ALL,[20] which has also to be studied in adults and in relapse cases.

Usually, none of the patients with *MLL-AF4* positive ALL express the CD20 antigen, which statistically constituted the main baseline difference between CD20-positive and CD20-negative cases in the present series. Taking into account the negative impact of *MLL-AF4* rearrangement observed in both childhood[21] and adult ALL,[22] this may have influenced the positive impact of CD20 expression observed in the pediatric St Jude series. Conversely, this cannot participate in the negative impact of CD20 expression reported in the present study.

In summary, the present study is the second to evidence the negative impact of CD20 expression in adult BCP-ALL, which reinforces the interest of evaluating rituximab combined to chemotherapy in adults with CD20-positive ALL. The MDACC has recently reported encouraging results with this combination in younger patients aged 30 years or under with CD20-positive ALL, as compared to historical experience.[23] In the ongoing GRAALL-2005 trial, our group is currently randomizing the adjunction of rituximab in adults with CD20-positive BCP-ALL aged 18-60 years.

Authorship and Disclosures

As members of the GRAALL Scientific Board, all authors participated actively in the study conception, design, and acquisition of data. M-CB centrally reviewed all immunophenotypic data. The statistical analysis was undertaken by HD. The manuscript was written by SM, M-CB, and HD and approved by all authors.

The authors declare no potential conflicts of interests.

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