Mixed Lineage Leukemia – Rearranged Childhood Pro-B and CD10-Negative Pre-B Acute Lymphoblastic Leukemia
Constitute a Distinct Clinical Entity

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Abstract

Purpose: Mixed lineage leukemia (MLL) abnormalities occur in ~50% of childhood pro-B acute lymphoblastic leukemia (ALL). However, the incidence and type of MLL rearrangements have not been determined in common ALL (cALL) and CD10+ or CD10− pre-B ALL.

Experimental Design: To address this question, we analyzed 29 patients with pro-B ALL, 11 patients with CD10− pre-B ALL, 23 pre-B, and 26 cALL patients with CD10 on 20% to 80%, as well as 136 pre-B and 143 cALL patients with CD10 ≥80% of blasts. They were all enrolled in four Austrian ALL multicenter trials. Conventional cytogenetics were done to detect 11q23 abnormalities and in parallel the potential involvement of the MLL gene was evaluated with a split apart fluorescence in situ hybridization probe set.

Results: We found that 15 of 29 pro-B ALL, 7 of 11 CD10− pre-B ALL, and 1 of 2 French-American-British classification L1 mature B-cell leukemia cases had a MLL rearrangement. However, no 11q23/MLL translocation was identified among the CD10+ pre-B and cALL patients. MLL-rearranged pro-B and CD10− pre-B ALL cases had similar clinical and immunophenotypic (coexpression of CDw65 and CD15) features at initial diagnosis.

Conclusions: The striking similarities between the two CD10− ALL subsets imply that CD10− pre-B ALL variants may represent pro-B ALL cases that maintained the propensity to rearrange and express their immunoglobulin heavy chain rather than actual pre-B ALL forms transformed at this later stage of B-cell differentiation. However, direct experimental data are needed to confirm this observation.

Rearrangements involving the mixed lineage leukemia (MLL) gene on chromosome band 11q23 represent nonrandom chromosomal abnormalities commonly found in human hematologic malignancies, including both acute lymphoblastic leukemia (ALL; 5-10%) and acute myeloid leukemia (AML; 5%; refs. 1, 2). Although the exact function of the MLL gene is unclear, it displays intrinsic histone methyltransferase activity and is known to play an important role in maintaining a cell type–specific expression of HOX genes, which are necessary for the cellular differentiation process (2, 3).

According to most published series, MLL-rearranged B-cell precursor (BCP) ALL can be reliably identified by a distinct immature CD10−/CD24− phenotype that is commonly characterized by the concurrent expression of the myeloid markers CDw65 and CD15, and of the chondroitin sulfate proteoglycan neuron-glial antigen 2 (NG2; refs. 4–7). Due to the observation that the translocation t(4;11) with its molecular counterpart, the MLL/AF4 fusion gene, is the most frequent MLL-specific aberration in infants with pro-B ALL, the CD10 negativity of MLL-rearranged BCP leukemia is commonly regarded as a sign of cellular immaturity (2, 8, 9). Furthermore, the coexpression of CDw65 and CD15 is taken as an evidence that this type of leukemia even represents a transformed upstream lymphomyelomonocytic progenitor cell.

As recent collaborative studies showed a marked clinical heterogeneity among MLL-rearranged ALL requiring distinct treatment approaches for different age groups and different 11q23/MLL translocations, it seems essential to screen for MLL abnormalities in pediatric ALL (10–12). Although the topic of MLL in other than the pro-B ALL subset has been recently

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addressed in adult BCP ALL, data on the frequency and type of MLL aberrations in childhood common ALL (cALL) or pre-B ALL are scarce (13).

Because 11q23/MLL abnormalities are not always detected by conventional cytogenetic procedures, the two preferred screening methods are reverse transcription-PCR (RT-PCR) and fluorescence in situ hybridization (FISH) analyses (14–20). The latter technology has the advantage that, using a dual-color MLL split apart probe set, it enables the detection of virtually all MLL involving aberrations on a single-cell level in a rapid and reliable manner. The respective fusion partners may then be identified in a second step by translocation-specific FISH probes or another molecular-genetic method.

In the present retrospective analysis, we determined the incidence and type of MLL aberrations in a large series of pediatric BCP ALL cases, including patients with pro-B, cALL, and pre-B ALL. Our particular aims were to assess whether MLL aberrations could be reliably predicted by a characteristic immunophenotype (to restrict the cohort of patients to be genetically screened) and whether they were actually restricted to a very immature BCP differentiation stage.

## Patients and Methods

### Patients.

Between April 1, 1990, and January 8, 2005, 772 previously untreated children and adolescents up to 18 years old diagnosed with ALL were included in three consecutive multicenter trials of the Berlin-Frankfurt-Münster (BFM) group: ALL-BFM-A (Austria) 1990 (n = 256), ALL-BFM-A 1995 (n = 230), and ALL-BFM-A 2000 (n = 286). From 1999 onward, infants with ALL were enrolled in trial INTERFANT-A 1999 (n = 8). ALL was diagnosed according to standard morphologic, cytochemical, and immunophenotypic criteria (21).

All cases were reviewed by the national study center in Vienna and patients were treated according to the respective BFM treatment protocols after obtaining written informed consent. Treatment stratification and protocols used in trials BFM-A 1990 and BFM-A 1995 have been summarized in detail elsewhere (22, 23). Of the 780 patients, 30 (4%) had a pro-B ALL, 476 (61%) a cALL, 175 (22%) a pre-B ALL, and 96 (12%) a T-ALL. In one patient, the MLL phenotype remained unspecified due to the lack of appropriate material and the remaining two patients had a mature B-cell acute leukemia (B-AL) with non–French-American-British (FAB) classification L3 morphology and no evidence of a C-MYC rearrangement.

### Materials and Methods

#### Cytogenetic and FISH analysis.

Cytogenetic analyses of tryptic/Giemsa–banded bone marrow preparations were done centrally according to standard procedures and results were classified according to the International System of Human Cytogenetic Nomenclature (1995).

MLL split apart interphase FISH analysis was also carried out centrally at the national study center according to standard procedures. In detail, the 167k13/ES4748 and the 217a21/ES4746 PAC clones, which were isolated from the RPCI-1 human PAC library and kindly provided by Ed Schuuring (Department of Pathology, University of Leiden, Leiden, the Netherlands), were used (20). The hybridization signal patterns of at least 200 nuclei were assessed in each case. A sample was considered positive if at least 6% of nuclei showed the respective abnormality pattern.

Details concerning the specific MLL/AF4 FISH assay have been described elsewhere (17). Screening for TEL/AML1 and BCR/ABL1 rearrangements were done with the commercial dual-color–labeled LSI TEL/AML1 ES (Vysis, Downers Grove, IL) and BCR/ABL1 (Quiogene, Middlesex, United Kingdom) fusion gene probe sets according to the recommendation of the manufacturer. A tricolor-labeled LSI IGH/MYC and CEP8 probe set (Vysis) was applied in the two mature B-AL cases to exclude a t(8;14)(q24;q32). The 13HH4 yeast artificial chromosome clone, which encompasses the entire MLL gene, and the AF9 RP11-173E6 clone (RPC1-11.CF, Invitrogen, Vienna, Austria) were used to verify a MLL/AF9 fusion gene in one patient (17).

#### MLL/AF4 RT-PCR, multiplex PCR, and long-distance inverse PCR.

Detailed protocols used for the assessment of the E2A/PBX1, BCR/ABL, BCR1/ABL, and MLL/AF4 fusion transcripts by RT-PCR and multiplex PCR to detect different MLL abnormalities have been described elsewhere (15, 16, 18, 24, 25). In addition, a newly established long-distance inverse-PCR method, allowing to detect any kind of MLL rearrangements if located within the breakpoint cluster region, was applied in cases of MLL abnormalities other than those detectable by FISH or RT-PCR (26).

#### Immunophenotypic analysis.

Before January 1, 1997, blast cells were analyzed microscopically at the national study center by standard indirect immunofluorescence assays with a panel of monoclonal antibodies directed against lymphoid- and myeloid-associated antigens. Between 1997 and 2000, mononuclear bone marrow cells were isolated by Lymphoprep (Axis-Shield Poc AS, Oslo, Norway) density gradient centrifugation, whereas thereafter nucleated bone marrow cells were prepared using a commercially available red cell lysing solution from An der Grub (Kaumberg, Austria)—Caltag Laboratories (Burlingame, CA). Analyses were centrally done on a dual-laser FACS Calibur (Becton Dickinson, San Diego, CA). Details regarding the test standardization, the data acquisition, and analysis with the CELL Quest software (Becton Dickinson) have been described elsewhere (27–31). Immunophenotypic subclassification was done according to the guidelines of the European Group for the Immunological Characterization of Leukemias (32). Criteria for immunophenotypic marker positivity were an expression on ≥20% of blasts for cell surface and on ≥10% of blasts for cytoplasmic and nuclear markers.

#### Statistical analysis.

Differences in the immunophenotypic expression patterns as well as clinical and laboratory variables were analyzed using the χ² test. Determination of sensitivity and specificity followed standard calculations. P values ≤0.05 were considered statistically significant.

### Results

#### MLL rearrangements in pro-B ALL cases.

Adequate material for molecular analysis was available in 29 of 30 (97%) patients with pro-B ALL. Twenty eight of 29 patients were screened by FISH and 14 had the MLL gene rearranged. Further molecular analysis identified 13 cases with a MLL/AF4 (FISH, n = 12; multiplex PCR, n = 1) and one patient with a MLL/AF9 (long-distance inverse-PCR) fusion gene. A single patient who could not be investigated by FISH had a MLL/AF4 rearrangement as shown by RT-PCR. None of the MLL-rearranged patients had a concurrent TEL/AML1, BCR/ABL, BCR1/ABL, or E2A/PBX1 fusion gene. Cytogenetic data were available in 24 of 29 patients (Table 1). In 10 of 14 MLL/AF4–positive patients, the t(4;11) was also detectable by conventional cytogenetics (sensitivity 71%).

#### MLL rearrangements in cALL, pre-B ALL, and mature B-AL cases.

Among the 684 patients with B-lineage ALL included in our study, we found 476 (70%) cases with cALL, 175 (26%) with pre-B ALL, and 2 with a mature B-AL with non-FAB L3 morphology and no C-MYC rearrangement. Because MLL rearrangements could be related to the expression status of
CD10, we further subdivided the patient cohorts according to their CD10 expression level.

Of the 175 pre-B ALL patients, 14 (8%) were CD10− and 161 (92%) CD10+. However, none of the CALL (per definition) or mature B-AL samples lacked the CD10 antigen. Adequate material for MLL analysis was available in 11 of 14 CD10− pre-B ALL cases. Somewhat surprisingly, 7 of 11 (64%) CD10+ pre-B ALL cases had a MLL rearrangement, including three with a FISH-verified MLL/AF4, two with a long-distance inverse-PCR–verified MLL/ENL, and another patient with a FISH-verified MLL/AF9 fusion gene. The remainder had a t(11;19)(q23;p13.3), but no material for confirmation of a MLL/ENL rearrangement. None of the 11 CD10− cases had a TEL/AML1, BCR/ABL, BCR1/ABL, or E2A/PBX1 rearrangement. Cytogenetic data were available in 10 of 11 CD10− pre-B ALL patients (Table 1). In five of seven MLL-rearranged CD10− cases, the type of 11q23 aberration was also identified on the cytogenetic level (sensitivity 71%).

Expression of CD10 was low (on 20-80% of blasts) in 25 of 161 (16%) CD10+ pre-B ALL cases, in 26 of all 169 (15%) CALL cases included in study BFM-A 2000, and in both cases of mature B-AL. No MLL translocation was detected in the 23 of 25 CD10low pre-B ALL cases with adequate material for analysis, including 21 who were screened by FISH and two by multiplex PCR. However, 3 of 23 patients had a FISH-verified TEL/AML1 and another four a RT-PCR-verified E2A/PBX1 rearrangement. In another patient (with constitutional trisomy 21) of this group, we found a 3’ MLL deletion in 74% of the interphase cells, which was found by long-distance inverse-PCR to have resulted from a novel fusion, including the MLL and BCL9L genes. BCL9L is located on 11q23 ~ 300 kb telomeric of MLL on the negative strand. It is thus not possible that the head-to-head fusion between MLL intron 8 and 3’-untranslated region of BCL9L could have generated a functional transcript. Possible alternative splicing variants involving genes located near the telomere on the positive strand still remain to be explored.

Out of the 26 CD10low CALL patients enrolled in study BFM-A 2000, those 16 without a TEL/AML1, BCR/ABL, BCR1/ABL, or E2A/PBX1 rearrangement were screened for MLL rearrangements. All of them tested negative. Among the two patients with a mature B-AL [one case with cy- and surface(s)-λ and one case with cy-κ/sIgM expression], a MLL/AF9 rearrangement was verified by long-distance inverse-PCR in the case expressing CD10 on 32% of blasts and lacking terminal deoxynucleotidyl transferase (TdT). However, no MLL abnormality was found in the other case (CD10 on 58% of blasts and TdT+).

Expression of CD10 was high (on ≥80% of blasts) in 136 of 161 (84%) CD10+ pre-B ALL cases and in 143 of all 169 CALL (85%) patients included in study BFM-A 2000. To limit the number of patients to be analyzed, 24 CD10high pre-B ALL cases were randomly selected for MLL FISH analysis. The selection was, however, restricted to the 95 of 136 patients, who were negative for TEL/AML1, BCR/ABL, BCR1/ABL, and E2A/PBX1. No MLL rearrangement was identified in these 24 CD10high pre-B ALL patients. In addition, none of the 113 patients with CD10+ pre-B ALL (irrespective of the CD10 expression level) included in studies BFM-A 1995 and 2000 had a cytogenetically evident 11q23 translocation or a MLL/AF4 fusion gene as evaluated by RT-PCR.

None of the 143 CD10high CALL patients enrolled in study BFM-A 2000 had a cytogenetically visible 11q23 translocation or a MLL/AF4 rearrangement as assessed by RT-PCR. Similarly, none of the patients with CALL (irrespective of the CD10

<table>
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<th>Karyotypes</th>
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<th>MLL− pre-B</th>
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<td>1 (10%)</td>
<td>2 (5%)</td>
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*Low hyperdiploidy: 47 to 50 chromosomes; high hyperdiploidy: 51 to 65 chromosomes.
expression level) included in trial BFM-A 1995 and having complete karyotypes (n = 113/146) had a cytogenetically visible 11q23 translocation or a RT-PCR-verified MLL/AF4 rearrangement. Hence, given our sensitivity of conventional cytogenetics of ~71% for detection of 11q23/MLL translocations as well as the exclusion of the most frequent type of rearrangement (MLL/AF4) by RT-PCR, we could anticipate an expected frequency of <1% for other MLL-involving translocations among (CD10 high) CALL. Thus, we did not further screen CALL patients by FISH.

Overall, the frequency of 11q23/MLL translocations was 55% among CD10- BCP ALL (15 of 29 pro-B ALL, 7 of 11 pre-B ALL), 2% among CD10low ALL (0 of 26 CALL, 0 of 23 pre-B ALL, and 1 of 2 mature B-ALL), and <1% among CD10high common (n = 143) and pre-B ALL cases (n = 136).

Clinical, phenotypic, and outcome data of the 29 pro-B and 58 pre-B ALL cases (including only patients analyzed by molecular genetics) according to the MLL and CD10 status. With respect to the clinical and laboratory variables at initial diagnosis (Table 2), MLL-rearranged pro-B ALL cases were significantly more often <1 year old (P = 0.003), had higher WBC counts (≥20,000/μL, P = 0.002; ≥50,000/μL, P = 0.005), and coexpressed CDw65 (P < 0.001) and CD15 (P = 0.024), compared with nonrearranged pro-B ALL patients. The expression of TdT, CD34, CD13, and CD33, however, did not differ between the two subgroups. Early response to treatment in peripheral blood on day 8 and in bone marrow on days 15 and 33 (end of induction therapy) were also not significantly different between the cohorts studied. For analysis of outcome, we excluded the patients enrolled in the ongoing trials BFM-A 2000 and INTERFANT-A 99, and thus found that 4 of 10 MLL-rearranged (all MLL/AF4-positive; bone marrow, n = 3; central nervous system, n = 1) and 1 of 9 (bone marrow) nonrearranged pro-B ALL patients had a relapse.

Comparison of the 11 CD10- pre-B ALL cases with the pooled subset of 47 pre-B ALL patients with either low or high CD10 expression revealed that the CD10- cases were significantly more often MLL rearranged (P < 0.001), <1 year old (P < 0.001), had higher WBC counts (≥20,000/μL, P < 0.001; ≥50,000/μL, P < 0.001), and coexpressed CDw65 (P < 0.001) and CD15 (P < 0.001; Table 2). Moreover, CD10- cases more commonly lacked TdT expression (P = 0.002) and showed a poor response to prednisone (P = 0.003) than CD10+ pre-B ALL cases. However, we found no differences regarding the other clinical variables, expression of CD34, CD13, and CD33 as well as early response to treatment on days 15 and 33. The analysis of outcome excluding the BFM-A 2000 and INTERFANT-A 99 patients showed that 2 of 9 CD10- (bone marrow, n = 2; one MLL/ENL-positive and one non-MLL-rearranged case) and 3 of 26 CD10+ pre-B ALL cases (bone marrow, n = 2; bone marrow and bone, n = 1) had a relapse.

Analysis of cases with other cytogenetically detectable 11q23 aberrations. All patients with other 11q23 aberrations were further clarified by FISH. In trial BFM-A 90, 125 of 160 (78%)
cALL patients had cytogenetic data available, including two children with a del(11)(q23). Due to the lack of material, only one patient could be further analyzed. FISH analysis showed the complete loss of one MLL signal and the presence of a TEL/AML1 rearrangement. Neither of the pro-B and pre-B ALL patients of trial BFM-A 90 had any other type of 11q23 aberration.

In trial BFM-A 95, 113 of 146 (77%) cALL patients had complete karyotypes, including two cases with a del(11)(q23). Both had a complete loss of one MLL signal and were TEL/AML1-positive, as revealed by FISH analysis. One pre-B ALL patient had a complex translocation t(1;9;11;19)(q21; p13; q12q23; p13). Comprehensive FISH and RT-PCR analyses displayed an underlying deletion of one MLL signal and the presence of an E2A/PBX1 fusion gene.

In trial BFM-A 2000, 164 of 169 (97%) cALL patients were completely karyotyped, including one patient who carried a translocation t(11;11)(q23;q33). Further evaluation by FISH showed the complete deletion of one MLL allele, and excluded a TEL/AML1 or E2A/PBX1 rearrangement. A pre-B ALL patient had a del(11)(q13q23) and FISH analysis disclosed the presence of a TEL/AML1 rearrangement, but no MLL- or BCL1-involving aberrations.

### Sensitivity and specificity of immunophenotypic markers in predicting MLL translocations among the 29 pro-B and 58 pre-B ALL cases (including only patients analyzed by molecular genetics)

We calculated the sensitivity and specificity of TdT, CD10, CDw65, CD15, CD13, CD33, and CD34 in predicting the presence of common MLL translocations. We analyzed these variables for the cohort of pro-B and pre-B ALL patients restricting the results to cases that have been examined for both markers CD15 and CDw65 (Table 3). CD10, CD13, and CD33 negativity as well as CDw65 positivity each showed a high sensitivity of 1.00. Specificities were 0.78, 0.11, 0.11, and 0.89, respectively. TdT negativity and CD15 positivity both achieved a high specificity of 0.93 and 0.98, but had a very low sensitivity of 0.17 and 0.44. Results were similar when the analysis was restricted to the pre-B ALL cases only (Table 3).

### Discussion

The identification of genetic abnormalities involving the MLL gene in pediatric ALL represents an indispensable prerequisite for the accurate classification of the leukemic disease because children with MLL-rearranged ALL usually have an increased risk of treatment failure (8–12, 33). Studies based on novel technologies, such as gene expression profiling, suggested that MLL-rearranged ALL is a highly distinct leukemia that can be clearly separated from other ALL subsets (34, 35). In particular, Armstrong et al. (34) showed that with respect to lymphoid- and myeloid-specific gene expression, MLL-rearranged ALL originates from an early hematopoietic progenitor cell expressing relatively low levels of CD10, CD24, and CD79b, but high levels of CD44, CD43, and distinct lineage-specific markers other than those expressed on lymphocytes.

Several previously published studies have already addressed the question of a characteristic immunophenotypic marker profile in MLL-rearranged BCP ALL (4–7, 36). However, data are rather heterogeneous and mostly not collected in a population-based fashion. Some authors restricted their analysis to infant ALL cases, others compiled pediatric and adult patients, or investigated a small number of cases only (4, 5, 7, 37). Indeed, a few studies indicated that the cyIgM+/CD10− phenotype may be associated with MLL aberrations. However, except for a recent study by Gleissner et al. (13) in adult ALL, none of these studies pointed out that the lack of CD10 expression may discriminate between MLL-rearranged and non-rearranged pre-B ALL cases (4–7, 13, 37).

As assessed in childhood ALL on a population-based scale, the most important finding of our analysis is that MLL-rearranged B-lineage ALL cases are almost always lacking significant CD10 expression, even if they express cyIgM, and thus represent rather matured BCP phenotypes (pre-B cell level). The only exception that we encountered was an infant suffering from a mature B-AL with FAB L1 morphology and a MLL/AF9 aberration (38). Whether the heterogeneous CD10 expression in this instance reflects an irregular differentiation of the MLL-rearranged cell population or whether only the CD10− blast cells carried the MLL rearrangement was not yet further investigated. On the other hand, we did not detect a single patient with any type of a MLL translocation among patients with CD10+ pre-B or cALL. However, it should be emphasized that the cutoff for marker positivity (on ≥20% blast cells) depends on the sensitivity of the methodology used for marker detection. It may well occur with newer flow cytometric laser systems or the usage of very bright fluorochromes that expression patters that would have been formerly classified as negative (on <20% blast cells) now appear as weakly positive.

As expected, the MLL/AF4 fusion gene was found to be by far the predominant type of a MLL aberration among pro-B ALL. However, among CD10− pre-B ALL cases, the MLL/ENL fusion gene occurred with a similar high frequency. Whether this may be due to the small number of patients studied or relate to a real biological basis has to be evaluated in future studies on

### Table 3. Sensitivity and specificity of immunophenotypic markers in predicting MLL rearrangements (including only patients analyzed by molecular genetics)

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<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>CD10 negativity</td>
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</tr>
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<td>CD13 negativity</td>
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<td>1.00</td>
<td>0.89</td>
</tr>
<tr>
<td>CD34 positivity</td>
<td>0.75</td>
<td>0.58</td>
</tr>
<tr>
<td>TdT negativity</td>
<td>0.17</td>
<td>0.92</td>
</tr>
</tbody>
</table>
larger series of MLL-rearranged CD10− pre-B ALL cases. In line with most reports, we found that the MLL-rearranged patients irrespective of their cyIgM status were frequently <12 months old and presented with high WBC counts at initial diagnosis (8–12, 33). Both subsets of CD10− BCP ALL were also more likely to coexpress the myeloid markers CDw65 and CD15.

Both CD10 negativity and CDw65 positivity showed a very high sensitivity of 100%, and a specificity of 78% and 89%, respectively, in predicting MLL rearrangements. The sensitivity of CD15 was less, but due to its high specificity and the fact that it exclusively occurred in conjunction with CDw65, a CD10−/CDw65+/CD15+ immunophenotype seemed to be most predictive for a MLL rearrangement. Previous data obtained with NG2, a further specific marker of MLL-rearranged leukemias, indicated that its frequency of expression in BCP ALL is similar to that of CDw65 and CD15 (4–7, 13, 36). Because the NG2 marker thus seemed to have no particular advantage in predicting MLL aberrations, we did not include it in our analysis. However, as has been already shown for NG2, we also found MLL-rearranged CD10− BCP ALL patients with no coexpression of CDw65 and CD15. Therefore, the most reliable screening marker to reduce a necessary genetic approach to a limited set of patients was found to be lack of CD10 expression. Other markers, including the myeloid antigens CD13 and CD33, and the stem cell marker CD34, did not differ significantly between the groups analyzed.

Overall, we noted that the clinical characteristics and immunophenotypic peculiarities of MLL-rearranged pro-B and pre-B ALL were largely identical. Because CD10 is always expressed on physiologic precursor B cells, the lack of its expression in MLL-rearranged pre-B ALL cases probably is a direct and specific consequence of this genetic alteration. In principle, the lack of CD10 expression may be due to an a priori suppression or a secondary down-regulation. The striking immunophenotypic and clinical similarities of both the MLL-rearranged pro-B and pre-B ALL cases provide convincing, albeit still circumstantial evidence, that they actually constitute a single biological entity. In this scenario, the MLL rearrangement will always take place in a susceptible progenitor cell at a particular stage of immature B-cell differentiation. Some of the transformed cells may then maintain the propensity to continue rearranging their immunoglobulin heavy chain genes and successful cell clones will eventually express cyIgM. However, this process will take place without experiencing the characteristic concomitant immunophenotypic steps of differentiation, such as CD10 expression, or even with aberrant down-regulation of CD10 expression. Although direct experimental evidence for this model is still lacking, the recent description of an analogous situation, namely the immunophenotypic maturation from the pro-B to the pre-B cell stage during the spontaneous in vitro differentiation of a cell line with a MLL/AF4 fusion gene, strongly supports the validity of this notion (39).

References


Mixed Lineage Leukemia—Rearranged Childhood Pro-B and CD10-Negative Pre-B Acute Lymphoblastic Leukemia Constitute a Distinct Clinical Entity

Andishe Attarbaschi, Georg Mann, Margit König, et al.


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