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B-cell precursor leukemias with MYC-rearrangement come into the limelight

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For a young fellow in pediatric hematology one of the mistakes that simply cannot be allowed to happen is the misclassification of Burkitt leukemia with FAB L3 morphology as B-precursor acute lymphoblastic leukemia (BCP-ALL). The intense, basophilic cytoplasm with prominent vacuolization of marrow blasts (but not necessarily in the peripheral blood) is easy to recognize and guides therapy towards short but very intensive pulses of chemotherapy based on cyclophosphamide, high-dose methotrexate, and cytosine arabinoside. This approach was developed in the 1980s of the last century by several study groups in Europe and the US, including the international Berlin-Frankfurt-Münster (iBFM) study group, and has shown tremendous success.¹⁻³ Previously, the patients, mostly children, succumbed to their leukemia due to very early relapses, usually while still under consolidation therapy.

There is an extremely high correlation between FAB L3 morphology, chromosomal translocations involving the *MYC*-locus at chromosome 8q24 and the mature B-cell developmental stage with surface Immunoglobulin (Ig) expression, so FAB L3 blasts became to be regarded as synonymous with mature B-cell, Burkitt-type leukemia with obligatory *MYC* activation. But sometimes things are not so simple, and *MYC* activation, be it by chromosomal translocation t(2;8), t(8;14) or t(8;22), respectively, has also been found in leukemias with a more immature, B-cell precursor phenotype (CD10⁺, CD19⁺, sIg⁻).^{4, 5} Although such cases are extremely rare, they are recurrently reported and always raise the extremely difficult clinical question of how to treat those patients: Should they receive ALL-type therapy with induction, consolidation followed by maintenance therapy or with rather short chemo-pulses with drugs that are particularly effective on very rapidly proliferating mature B-cells? In this issue, Bomken and colleagues⁶ address this question and molecularly characterize the largest collection of cases worldwide with unprecedented completeness and accuracy.

Encompassing 30 years of registration (1989-2019), their study is remarkable in several ways:

First, it is impressive simply by its huge number of cases (n=90) and shows the power of large international collaborations across study groups, countries and even continents. This effort allowed them to sub-group BCP-ALLs with *Ig-MYCr* rearrangement (*Ig-MYCr*) into three different categories, one where other, classical BCP-ALL-typical genetic aberrations occurred concurrently with the *Ig-MYCr*, one with a combination of *Ig-MYCr* and *BCL2/BCL6* rearrangement and one where *Ig-MYCr* was the defining and sometimes even sole genetic aberration. In agreement with other studies, the relapse-free survival of children or adults with double or even triple hit disease (*Ig-MYCr* + *BCL2* +/- *BCL6*) was below 25% at two years, making this group available for other experimental approaches.

Second, Bomken et al⁶ went on to use RNAseq, whole exome and targeted sequencing as well as methylation arrays in a subset of cases and demonstrated the power of these modern

molecular tools. Mutational analysis subdivided these *Ig-MYCr* cases into those with ALL-typical mutations (e.g. affecting the *IKZF1* or *KRAS* gene) and those with “Burkitt-type” mutations (including *ID3*, *TCF3*). Perhaps unsurprisingly, they also identified hidden and previously overlooked aberrations specifically seen in BCP-ALL, e.g. three patients with an *IgH-DUX4* rearrangement.⁷ For those cases, at least, the therapeutic dilemma seems to be solved since they can safely continue to follow BCP-ALL protocols. The mutational part of the article by Bomken et al⁶ fits well to another recent study in which Burkitt lymphoma (BL) with immature B-cell immunophenotype were molecularly more similar to BCP-ALL than to classical BL.⁸

Third, as shown in Figure 5 of their paper, Bomken et al⁶ did not find major differences in survival between patients who stayed on therapy for BCP-ALL and those who were taken off protocol. One caveat of the study lies in the unavailability of data regarding treatment for those patients taken off-protocol as well as clinical and laboratory data such as LDH, uric acid, tumor lysis parameters, and blast morphology. It would have been extremely interesting to know how they were treated and how did they look like clinically. Of note is another publication by Herbrueggen et al⁹ where they reported on 14 patients with pre-B lymphoblastic lymphomas (eight with unquestionable L3 morphology, three with mixed L1/L3 morphology and three unclassified) and finally recommended therapy according to mature B-cell NHL with intensive, short treatment courses. However, in four cases of this study, the treating centre combined mature B-cell therapy with subsequent maintenance therapy pointing again to the difficulties in determining an overall strategy. In their truly outstanding study of a very rare entity, Bomken et al⁶ finally recommended to include *Ig-MYCr* patients in ALL trials and uniform registration and treatment would be of major benefit in gaining further insights. Some patients who were taken-off protocol were absent from further investigation and likely received unproven, individualized treatment. We agree with their conclusion, cases with BCP-ALL-specific features and the often subclonal *Ig-MYCr* (often only identified molecularly), should be considered as BCP-ALL. Nevertheless, the results of the study by Herbrüggen et al⁹ raise some doubts as to whether the decision about the appropriate

therapy should not also take into account the other clinical parameters mentioned above. This particularly affects those patients who harbor *Ig-MYC* as the only and defining aberration. Between 20-30% of patients with available clinical data showed initial CNS involvement, a relatively high proportion that exceeds the percentage commonly seen in BCP-ALL, but more commonly seen in Burkitt leukemia.¹⁰

In addition, the cascade of disease recurrences is reminiscent of Burkitt leukemia and BL, since almost all recurrences occurred very early on. This underscores another paradigm in pediatric hematology young fellows learn: if patients survive this disease for 2 years, they can be considered definitively cured.

References:

1. Reiter A, Schrappe M, Ludwig WD, et al. Favorable outcome of B-cell acute lymphoblastic leukemia in childhood: a report of three consecutive studies of the BFM group. *Blood*. 1992;80(10):2471-2478.
2. Patte C, Philip T, Rodary C, et al. Improved survival rate in children with stage III and IV B cell non-Hodgkin's lymphoma and leukemia using multi-agent chemotherapy: results of a study of 114 children from the French Pediatric Oncology Society. *J Clin Oncol*. 1986;4(8):1219-1226.
3. Murphy SB, Bowman WP, Abromowitch M, et al. Results of treatment of advanced-stage Burkitt's lymphoma and B cell (Slg+) acute lymphoblastic leukemia with high-dose fractionated cyclophosphamide and coordinated high-dose methotrexate and cytarabine. *J Clin Oncol*. 1986;4(12):1732-1739.
4. Navid F, Mosijczuk AD, Head DR, et al. Acute lymphoblastic leukemia with the (8;14)(q24;q32) translocation and FAB L3 morphology associated with a B-precursor immunophenotype: the Pediatric Oncology Group experience. *Leukemia*. 1999;13(1):135-141.
5. Sakaguchi K, Imamura T, Ishimaru S, et al. Nationwide study of pediatric B-cell precursor acute lymphoblastic leukemia with chromosome 8q24/MYC rearrangement in Japan. *Pediatr Blood Cancer*. 2020;67(7):e28341.
6. Bomken S, Enshaei A, Schwalbe EC, et al. Molecular characterisation and clinical outcome of B-cell precursor acute lymphoblastic leukaemia with IG-MYC rearrangement. *Haematologica*. 2022;xxx.
7. Lilljebjorn H, Henningsson R, Hyrenius-Wittsten A, et al. Identification of ETV6-RUNX1-like and DUX4-rearranged subtypes in paediatric B-cell precursor acute lymphoblastic leukaemia. *Nat Commun*. 2016;7:11790.
8. Wagener R, Lopez C, Kleinheinz K, et al. IG-MYC (+) neoplasms with precursor B-cell phenotype are molecularly distinct from Burkitt lymphomas. *Blood*. 2018;132(21):2280-2285.
9. Herbrueggen H, Mueller S, Rohde J, et al. Treatment and outcome of IG-MYC(+) neoplasms with precursor B-cell phenotype in childhood and adolescence. *Leukemia*. 2020;34(3):942-946.
10. Salzburg J, Burkhardt B, Zimmermann M, et al. Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: a Berlin-Frankfurt-Munster Group Report. *J Clin Oncol*. 2007;25(25):3915-3922.