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 French-American-British (FAB) classification 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 USA, including the international Berlin-Frankfurt-Münster 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 strong 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), 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 reported recurrently 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 of *Haematologica*, Bomken and colleagues[6] 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 subgroup BCP-ALL with *IG-MYC* rearrangement (*IG-MYC*-r) into three different categories, one in which other, classical BCP-ALL-typical genetic aberrations occurred concurrently with the *IG-MYC*-r, one with a combination of *IG-MYC*-r and *BCL2/BCL6* rearrangement and one in which *IG-MYC*-r 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-MYC*-r + *BCL2* ± *BCL6*) was below 25% at 2 years, making this group available for other experimental approaches.

Second, Bomken *et al.*[6] went on to use RNA-sequencing, 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-MYC*-r cases into those with ALL-typical mutations (e.g., affecting the *IKZF1* or *KRAS* gene) and those with "Burkitt-type" mutations (including *ID3* and *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 al.*[6] fits well with another recent study in which Burkitt lymphomas (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 al.*[6] 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 lactate dehydrogenase and uric acid levels, tumor lysis parameters, and blast morphology. It would have

been extremely interesting to know how these were treated and how they looked like clinically. Another publication by Herbrueggen *et al.*[9] is worth noting: the authors reported on 14 patients with pre-B lymphoblastic lymphomas (8 with unquestionable L3 morphology, 3 with mixed L1/L3 morphology and 3 unclassified) and finally recommended therapy according to mature B-cell non-Hodgkin lymphoma protocols with intensive, short treatment courses. However, in four cases of this study, the treating center combined mature B-cell therapy with subsequent maintenance therapy pointing again to the difficulties in determining an overall strategy. At the end of their truly outstanding study of a very rare entity, Bomken *et al.*[6] recommended including *IG-MYC*-r patients in ALL trials; uniforming registration and treatment would be of major benefit for gaining further insights. Some patients who were taken off protocol were absent from further investigation and likely received unproven, individualized treatment. We agree with the authors' conclusion, cases with BCP-ALL-specific features and the often subclonal *IG-MYC*-r (often only identified molecularly), should be considered as BCP-ALL. Nevertheless, the results of the study by Herbrüggen *et al.*[9] do 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 is particularly relevant to those patients who harbor *IG-MYC*-r as the only and defining aberration. Between 20-30% of patients with available clinical data showed initial central nervous system 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 that young fellows learn: if patients survive this disease for 2 years, they can be considered definitively cured.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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