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 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 sub-group BCP-ALLs with Ig-MYC 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 al\(^6\) 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. 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 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.

Third, as shown in Figure 5 of their paper, Bomken et al 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 they look like clinically. Of note is another
publication by Herbrueggen et al 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 al finally recommended to include Ig-MYCr patients in
ALL trails 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 al 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-MYCr 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.\textsuperscript{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: