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CML-like biology: BCR::ABL1 and beyond...

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In this issue of *Haematologica*, van Outersterp and colleagues report the case of a child first diagnosed with B-cell precursor acute lymphoblastic leukaemia (ALL) at the age of two, who relapsed three years later with different immunoglobulin (IG) and T-cell receptor (TCR) rearrangements. At relapse, an ABL-class fusion, *CCDC88C::PDGFRB*, was identified as the primary genetic lesion – and could be successfully retrospectively identified as primary aberration also in the initial diagnosis.[1]

Although, owing to the retrospective nature of the study and limited availability of material, the depth of analyses was limited, the authors provide convincing evidence that the primary aberration – here an ABL-class fusion – was present within a broader haematopoietic clone extending beyond the lymphoid lineage. It was only after the acquisition of additional, secondary lesions (genomic losses involving e.g. *PDE4B*, *RUNX1*, *TOX*), differing between diagnosis and recurrence, that a fully leukaemic ALL clone emerged. The biology and clonal architecture therefore resemble those of the recently recognised subtype of ALL assigned chronic myeloid leukaemia (CML)-like (CML-like) disease (also referred to as BCR::ABL1-positive B-ALL with multilineage involvement*).*[2,3]

The patient described is part of a previously reported cohort of 22 patients harbouring non-*BCR::ABL1* ABL-class fusions[4], and another study presented 21 such patients.[5] Importantly, this child was the only one across both series to show discordance between quantitative monitoring of genomic levels of the ABL-class fusion and IG/TR rearrangements during therapy. This suggests that such cases are relatively rare among non-*BCR::ABL1* ABL-class positive leukaemias – 1 in 43 (2.3%) compared with up to one-third of *BCR::ABL1*-positive ALL[3]. Nonetheless, it clearly confirms that the phenomenon can indeed occur outside the *BCR::ABL1* context.

This case report raises several thought-provoking questions. I will highlight just two of them here.

The first relates to molecular monitoring of minimal residual disease (MRD) in ALL and the choice of clonal markers. In routine practice, MRD assessment relies primarily on IG/TR gene rearrangements. This approach is well standardised, validated and incorporated into virtually all treatment protocols. However, these rearrangements do not necessarily capture the entire malignant or aberrant clone – owing to subclonality, ongoing IG/TR rearrangements during treatment, or, as in this case, specific aspects of disease biology. Previous work has shown that a "pre-leukaemic clone", marked by the presence of a primary aberration but lacking additional mutations required for full transformation, may persist even after eradication of clinically overt leukaemia.[6-8] Such clones can serve as a reservoir of potentially dangerous cells, capable of giving rise to recurrence following a "new second hit", though such recurrence may not represent a classical relapse. This biology has been described in *ETV6::RUNX1*-positive ALL[6,7] and in *BCR::ABL1* CML-like ALL[8] – and now appears to extend to other ABL-class fusions as well.[1] Whether this phenomenon is more common in ALL remains uncertain, but comprehensive monitoring of both the primary genetic lesion and IG/TR rearrangements (or other clone-specific markers) seems to be a way to uncover it. Whereas until recently tracking primary aberrations at the DNA level was technically challenging, advances in and growing accessibility of sequencing approaches, including whole-genome sequencing, are rapidly changing this landscape – as we can already see e.g. in acute myeloid leukaemia.[9]

A second important issue is whether some of the pressing clinical questions we have recently been facing in *BCR::ABL1*-positive ALL – particularly in CML-like cases – may also be relevant to other ABL-class fusions. One such dilemma arises at the end of frontline therapy: how should we proceed when markers of the fully transformed leukaemic clone (typically patient-specific IG/TR rearrangements, sometimes others) have long been negative, but the primary aberration (*BCR::ABL1* or another ABL-class fusion) remains detectable?[8,10] Thoughts on this topic are hampered by the fact that, especially historically, such patients were not monitored further, and even today, their follow-up after completion of the protocol is definitely not routine. Therefore, there is still a lack of extensive data,

but we are trying to fill these gaps with individual pieces of information and through active international cooperation. However, broadly speaking, three strategies can be considered: (i) a "watch and wait" approach, with regular MRD monitoring but no active intervention; (ii) continuation of targeted therapy, usually by tyrosine kinase inhibitors (TKIs), possibly in combination with immunotherapy; or (iii) identification of a donor and proceeding to allogeneic transplantation in the first remission.

Each option has advantages and drawbacks. On the one hand, there is the risk of recurrence, whether as a classical relapse of the original clone or as a "new" leukaemia arising from a reservoir of pre-leukaemic cells – as illustrated both here and in CML-like *BCR::ABL1*-positive cases[1,8]. On the other hand, long-term TKI therapy carries non-negligible toxicity, particularly in children. Moreover, clinical experience (including this case) suggests that TKIs alone rarely achieve a meaningful reduction or eradication of the pre-leukaemic clone[1,8,10] – most likely because these cells, unlike fully transformed leukaemic cells, are not dependent on the aberrant kinase for survival, and thus are relatively unaffected by its pharmacological inhibition at the protein level. Whether the continued TKI treatment at least decreases the risk of clinical recurrence remains to be established. Targeted immunotherapies are another possibility, but those directed against lymphoid markers (e.g. anti-CD19, anti-CD22) are of limited efficacy here, since in CML-like leukaemias at least part of the aberrant clone resides outside the lymphoid lineage. Transplantation therefore probably remains the only option offering the possibility of a complete cure. Yet recommending it in a patient in morphological remission, often without clinical signs of disease – and who would appear entirely healthy if the primary aberration were not being monitored – is far from a straightforward and easy decision. Should recurrence occur, however, the scenario changes markedly, and a second remission still offers a reasonable chance of successful transplantation.

We have already offered some recommendations[8], but, as mentioned above, robust conclusions will require collection and integration of more cases – both with *BCR::ABL1* and with other ABL-class fusions. Efforts are under way to organise and coordinate this process, but only through close collaboration with colleagues across centres and countries — which is essential given the relative rarity of these cases — will we be able to build sufficiently robust, evidence-based guidance for tackling these challenging situations.

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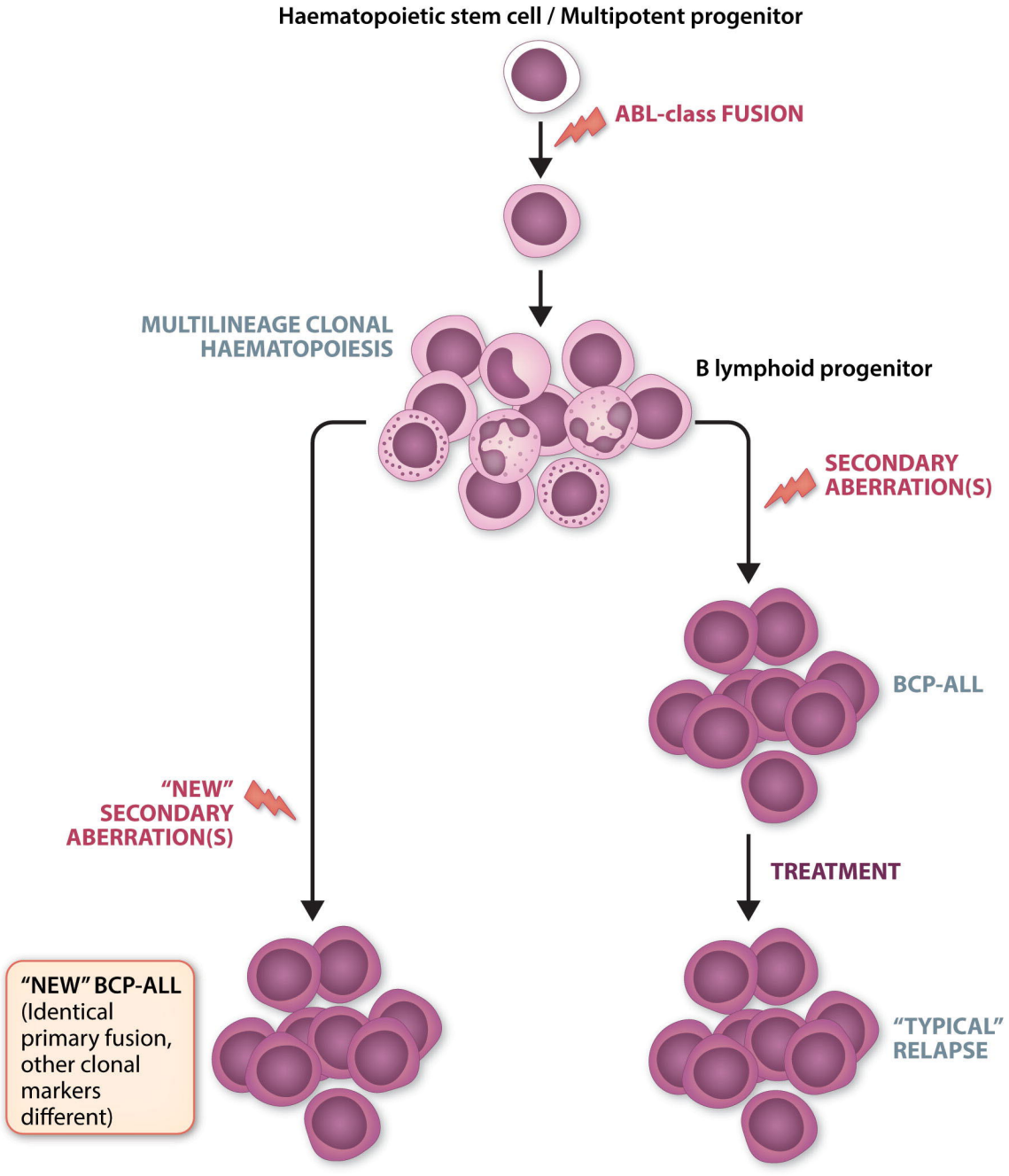
Figure:

The origin of "CML-like" leukemia (initiated by *BCR::ABL1* or another ABL-class fusion) and two different types of disease recurrence.


Haematopoietic stem cell / Multipotent progenitor
ABL-class FUSION
MULTILINEAGE CLONAL HAEMATOPOIESIS
B lymphoid progenitor
SECONDARY ABERRATION(S)
BCP-ALL
TREATMENT
"TYPICAL" RELAPSE
"NEW" SECONDARY ABERRATION(S)
"NEW" BCP-ALL (Identical primary fusion, other clonal markers different)