Comment on "Acute pro-B-cell lymphoblastic leukemia evolving from myelodysplastic neoplasm post cytotoxic therapy: a case report"

It was a pleasure to read the meticulously prepared case report by Wobst *et al.*,[1] published in the recent issue of Haematologica. The authors convincingly demonstrated the clonal evolution of a pro-B acute lymphoblastic leukemia (ALL) in an 80-year-old patient following long-lasting therapy with lenalidomide/dexamethasone (21 cycles) more than 12.5 years earlier because of a previous multiple myeloma (MM) diagnosis. In between this 12.5-year span, the patient developed a myelodysplastic syndrome (MDS) post cytotoxic therapy (MDS-pCT) with a chromosome del 20q and a presumably pre-existing *DNMT3A* mutation. The authors claimed that the pro-B-ALL directly developed from the MDS-pCT clone by gaining additional chromosomal aberrations such as loss of one X-chromosome (-X) or gain of chromosome 14q (+14q). While the superbly presented fluorescense *in situ* hybridization data support this conclusion, there are some things however, that may have escaped the authors' attention. Chiefly amongst these are the subtleties incurred by lenalidomide treatment on IKAROS 1 and 3 degradation.[2] In a series of intricate biochemical steps, lenalidomide leads to ubiquitination and proteasomal degradation of these key lymphoid transcription factors in B-cell precursors, which exactly mimics the situation observed in B-ALL. Genetic *IKAROS* alterations - either germline or somatically acquired - are key drivers in B-ALL development.[3-5] In turn, the lenalidomide-accompanying block in B-cell maturation is, at least in part, closely linked to its therapeutic efficiency in MM.[2] Thus, it is quite likely that lenalidomide therapy increases the intrinsic risk for subsequent B-ALL development,[6] regardless of any MDS-pCT development. Along these lines, I would like to draw the attention of the scientific community to the work of Fürstenau *et al.*,[7] who recently described that three of 56 patients, who had been exposed to lenalidomide, subsequently developed B-ALL. In one of these patients, Fürstenau *et al.*, demonstrated a common B-cell origin chronic lymphocytic leukemia (CLL) and B-ALL. Interestingly, this patient also had a *DNMT3A* mutation, which was also observed in the patient described by Wobst *et al*. Unfortunately in the latter case however, it was not possible to compare the side-by-side IgH status of the MM and the pro-B-ALL since material was not available from the MM.

In summary, biochemical data supports the causal link between IKAROS degradation and lenalidomide-associated B-ALL. This hypothesis is also strengthened by recent observations of patients in whom lenalidomide discontinuation alone led to regression of incipient or overt B-ALL clones, even without any further B-ALL therapy.[8] The latter observation calls for novel B-ALL therapies in which restoration of endogenous IKAROS levels is achieved. Pre-clinical data in animal models showed that this approach is very promising, particularly in Philadelphia chromosome-positive (Ph+) and Ph+-like B-ALL, where sustained disease remission was observed following IKAROS re-engagement.[9]

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Disclosures

No conflicts of interest to disclose.

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