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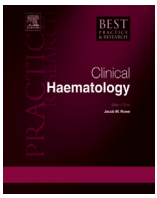

6

Can we say farewell to monitoring minimal residual disease in acute promyelocytic leukaemia?

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Molecularly targeted therapies have transformed the management of *PML-RARA*+ acute promyelocytic leukaemia (APL), with survival rates now exceeding 80% in clinical trials. This raises questions about the relevance of post-remission monitoring for *PML-RARA* transcripts, which has been widely used to predict relapse, guiding early intervention to prevent disease progression and the inherent risk of fatal bleeding. Given the treatability of haematological relapse, survival benefits would only be seen if monitoring could identify patients who could be salvaged if treated early but not later on, although it could be argued that early deployment of arsenic trioxide (ATO) can avoid inducing hyperleucocytosis and the associated differentiation syndrome, which frequently complicate treatment of frank relapse. However, given the low rates of relapse now observed in patients presenting with standard risk disease (i.e. presenting WBC $<10 \times 10^9$/l) who achieve early molecular remission, subsequent sequential minimal residual disease (MRD) monitoring confers only a marginal benefit, so could be avoided in this group. However, sequential MRD monitoring may still be of value in patients with high risk APL, although evidence tends to come from historically controlled studies. Therefore, there may remain a role for MRD monitoring in the most clinically challenging subsets of APL, but the continuing debate

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highlights the need for robust evidence in developing a more individualized approach to management of other subtypes of acute leukaemia.

Molecular diagnosis of APL

Acute promyelocytic leukaemia (APL) is characterised by chromosomal rearrangements involving the *RARA* locus at 17q21 encoding the myeloid transcription factor Retinoic Acid Receptor Alpha (reviewed [1]). In the majority of APL cases (~98%) *RARA* is fused to the *PML* locus at 15q22, typically due to the t(15;17)(q22;21), but in ~10% of APL the classical t(15;17) may be absent, with the *PML–RARA* fusion resulting from an insertion event or more complex rearrangements [2]. Rarely *RARA* is fused to an alternative partner, with *PLZF* (*ZBTB16*), *NPM1* and *STAT5b* located at 11q23, 5q35 and 17q21 being the most frequent [1]. The nature of the fusion partner has a critical bearing on the response to molecularly targeted therapies, namely all *trans*retinoic acid (ATRA) and arsenic trioxide (ATO), underlining the importance of molecular diagnostics for appropriate disease management [3]. ATO has been shown to bind to the PML moiety of the PML-RARα oncoprotein, leading to post-translational modification (SUMOylation) and targeted degradation by the proteosome (reviewed [4]). Accordingly, ATO activity is restricted to PML-RARα associated APL; ATRA activity extends to cases with fusions involving NPM1, NUMA and FIP1L1, whereas APL cases involving PLZF and STAT5b are resistant and have been associated with a poorer prognosis [1,5].

In addition to identifying patients likely to benefit from targeted therapies, molecular analysis using reverse transcriptase polymerase chain reaction (RT-PCR) assays has been considered a standard component of the diagnostic work-up of cases of suspected APL, serving to identify the fusion partner and chromosomal breakpoint location necessary to determine the most appropriate assay for tracking minimal residual disease (MRD) in any given individual [3]. In the majority of cases with the t(15;17), the reciprocal *RARA–PML* fusion transcript is coexpressed, which can be used as an additional and potentially more sensitive target to track MRD in parallel with the standard *PML-RARA* assay [6,7] (Fig. 1).

Rationale for MRD monitoring in APL

The introduction of ATRA into anthracycline-based chemotherapy treatment schedules led to a significant increase in overall survival rates (Fig. 2) over the last 25 years. The current good outcomes present a challenge as to how further improvements might be achieved. One aspect that remains a

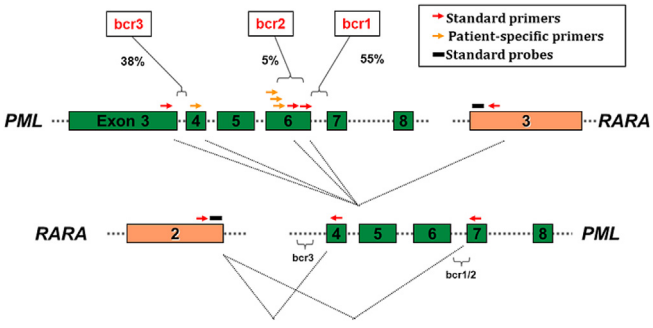

Fig. 1. Design of real-time quantitative polymerase chain reaction assays to track MRD in APL. See Ref. [7] for further details, including primer and probe sequences.