Current treatment of acute promyelocytic leukemia
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According to well established evidence, modern treatment of newly diagnosed acute promyelocytic leukemia (APL) should consist of all-trans retinoic acid (ATRA) and concomitant anthracycline-based chemotherapy. In fact, a number of large multicenter trials including high numbers of patients with prolonged follow-up have clearly shown that this approach allows cure of the disease in more than 75% of cases. Current consensus also indicates that APL should be managed by a risk-adapted approach essentially based on leukocyte number at presentation, whereby patients with leukocyte counts greater than 10 x 10^9/L should receive more intensive treatment including, for example, cytosine arabinoside. The type of anthracycline and whether it should be combined or not with other agents, such as cytosine arabinoside in standard risk patients remain controversial. Other issues which are still matter of investigation include the role of novel active compounds such as arsenic trioxide (ATO) and in particular its efficacy in the long-term, and the optimization of molecular monitoring of residual disease by reverse transcriptase polymerase chain reaction (RT-PCR), whose clinical relevance for better assessment of response to treatment is beyond question. Several prospective studies using qualitative RT-PCR of the disease-specific PML/RARα hybrid gene have demonstrated that the achievement of molecular remission after completion of consolidation is associated with prolonged survival, whereas persistence of, or conversion to, PCR-positivity in bone marrow after consolidation correlates strongly with subsequent hematologic relapse. Thus, the achievement of molecular remission is nowadays considered as a therapeutic objective in the management of APL. The recent development of real-time quantitative PCR (RQ-PCR) techniques provides an opportunity to determine at the quantitative level the kinetics of PML/RARα reduction or increase in the individual patient. Moreover, compared to the qualitative assay, RQ-PCR allows better identification of poor quality RNA and facilitates the standardized analysis of samples in multi-center clinical trials.

Although the standard ATRA plus chemotherapy combination has dramatically improved the disease prognosis, treatments fail in about 25% of APL patients reported in most recent studies due to early death or relapse. Moreover, these conventional treatments are associated with significant hematologic toxicity due to myelosuppression, and with serious, though infrequent late complications such as the occurrence of secondary myelodysplastic syndromes and/or acute myeloid leukemias. Current investigations aimed at optimising treatment of newly diagnosed APL include the use of less toxic and highly effective agents such as ATO and the possibility of more accurate and stringent molecular monitoring of minimal residual disease (MRD) offered by the RQ-PCR technique.

In this issue of the journal, Santamaria et al. report on the longitudinal monitoring by RQ-PCR in APL patients. Considering the timing of sampling, the authors found no correlation between RQ-PCR transcript levels, with the most significant correlation being found during follow-up (only three positive cases were detected at the end of consolidation time point). These data, which are in line with those reported in previous studies, further strengthen the clinical value of molecular monitoring in the post-consolidation phase, whereas early (post-induction) results are not informative for therapy adaptations. In fact, molecular data after consolidation and during follow-up not only to therapy to be anticipated in patients at risk of relapse, but also spare patients who are presumably cured or at very low risk of relapse from unnecessary toxicity. Using RQ-PCR, some degree of uncertainty remains on the significance of low PML/RARα transcript numbers (between 1 and 10 normalized copy numbers). In these latter cases, running in parallel the conventional qualitative PCR test characterized by relatively low sensitivity (10^-3-10^-4 approximately) is helpful because it may provide more informative data as remarked by Santamaria et al.

Based on several studies showing its striking activity in relapsed patients, ATO has been licensed for the treatment of relapsed and refractory APL. Although the mechanism of action of ATO in APL is complex and not yet known in detail, it induces apoptosis in vitro through caspase activation, while a lower ATO concentration produces partial differentiation of leukemic promyelocytes through PML/RARα degradation. ATO is usually well tolerated, although its use is associated with a series of adverse events including hyperleukocytosis, the APL differentiation syndrome and prolongation of the QT interval. Remarkably, unlike ATRA, ATO alone is able to induce molecular remission in more than 85% of patients, thus representing the most effective single agent available in this disease. In keeping with this clinical observation, Zheng et al. report in this issue of the journal a study suggesting that ATO is able to eliminate the PML/RARα-positive leukemic stem cells.
Using murine Sca1+/lin- hematopoietic stem cells retrovirally transduced to express PML/RARα, the authors show that these cells maintain their replating efficiency and capacity to engraft in vivo after exposure to ATRA, whereas the self renewal potential of Sca1+/lin- stem cells is abrogated following treatment with ATO. While this investigation gives further support to the notion that ATO as a single agent is potentially curative in APL, it is important to remember that ATO and ATRA have been shown to be synergic in vivo providing better results than either agent used as monotherapy in the clinical setting.

Several investigators have recently reported promising, though preliminary, results using ATO in front-line APL therapy. These data need to be strengthened by analysis of larger series and by more prolonged observation in appropriately designed randomized trials for newly diagnosed APL.

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