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Development and overcoming of ATRA resistance in acute promyelocytic leukemia

Despite the fact that virtually 100% of patients with genetically proven, PML/RARα-positive acute promyelocytic leukemia (APL) are responsive to all-trans retinoic acid (ATRA), this agent is per se unable to eradicate the leukemic clone, such that a status of minimal residual disease remains detectable during remission by conventional RT-PCR assays, and clinical relapse almost invariably occurs in all patients receiving ATRA monotherapy.[1] This evidence provided the rationale for modern treatment approaches with combined ATRA and chemotherapy which currently result in long-lasting molecular remission and potential cure in the majority of patients.[2]

The phenomenon of ATRA resistance in APL has interested numerous investigators and several mechanisms have been proposed to explain its development, such as: i) reduced plasma concentrations following prolonged administration; ii) enhanced intracellular sequestration by the cellular retinoic acid binding protein (CRABP); iii) absence of ATRA-induced PML/RARα degradation, and iv) emergence of leukemic cells with functional defects of the PML/RARα protein including mutations in the ligand binding domain (LBD).[2-8] Initially described in a cell line subclone,[5] such mutations, which would abrogate or impair ligand binding to the target receptor, were subsequently identified in fresh blasts collected at the time of clinical relapse from a few ATRA-resistant APL patients.[6,7]

In this issue of Haematologica, Marasca *et al.*[9] describe two patients with acquired ATRA resistance who, at relapse, showed mutations in the LBD of PML/RARα, leading in both cases to amino acid substitutions. In one patient, the authors report a previously unrecognized point mutation which would also predict for alteration in the ligand binding capacity, thereby providing a suggestive molecular explanation for the clinical resistance to ATRA. Most importantly, Marasca *et al.*[9] report for the first time the overcoming of ATRA resistance in patients with mutated LBD of PML/RARα by use of arsenic trioxide. This latter agent was found to induce apoptosis rather than differentiatiation by selectively targeting the same PML/RARα fusion protein *in vitro* in ATRA-resistant patients' blasts.[8] The achievement of remission in these two cases provides further compelling evidence of non-cross resistant effectiveness of this agent, with respect to ATRA, in the treatment of APL.

A number of clinical and biologic issues remain to be addressed by future investigations on ATRA resistance in APL. First, the incidence of PML/RARα LBD mutation in relapsing patients is presently unknown and too few cases have been characterized to date. Second, although preliminary in vitro studies using site-directed mutagenesis indicate a pathogenetic link between PML/RARα LBD mutations and altered binding of the ligand,[10] it is presently unclear to what extent these molecular changes would determine clinical resistance to ATRA *in vivo*. In a substantial proportion of APL patients, disease relapse is in fact still responsive to ATRA and long-term remission is achieved after ATRA reinduction followed by intensive consolidation.[2] Finally, clinical observations clearly indicate that the likelihood of response to salvage treatment with ATRA is inversely proportional to the duration of first remission and in particular to the time period during which patients have been off ATRA.[2] This would rather favor the pharmacokinetic theory,[3] according to which adequate plasma concentrations might be reinstored after prolonged discontinuation of the drug. Do patients with late relapse harbor PML/RARα LBD mutaions as well? What is the effect of anthracyclines on mutated subclones? Are they as effective as arsenic trioxide? At the biologic level, one intriguing question is whether these alterations are already present at the time of diagnosis or whether, alternatively, they are events acquired during the clinical evolution of the disease. In the former instance, subclonal mutations might simply be undetectable at presentation due to the limited sensitivity of our PCR assays and they would become identifiable subsequently following clonal selection favored by a proliferative advantage of mutated cells. Mutations acquired after initial diagnosis might be the consequence of genomic instability, cytotoxic treatment or both.

Combined with clinical investigation, more extensive biochemical and molecular studies on APL relapses should allow better understanting of ATRA resistance development and might provide important therapeutic indications for overcoming it.

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Treatment of myelodysplastic syndromes

Recent articles in this journal have analyzed etiology, pathogenesis, diagnosis and treatment of myelodysplastic syndromes (MDSs).[1-11] A meta-analysis of available studies has showed that the only two treatments that can prolong survival are allogeneic stem cell transplantation (SCT) and intensive chemotherapy, although only a minority of MDS patients can really benefit from them.[10]

In this issue Santini and Giles[12] analyze the potential of amifostine in the treatment of MDSs. There are great expectations about this drug, but – as the authors underline – prospective randomized clinical trials are needed to establish the real usefulness of amifostine.

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