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Acute Promyelocytic Leukemia – From Molecular Changes to High Effective Treatment

Monika Podhorecka* and Arkadiusz Macheta

Department of Hematooncology and Bone marrow Transplantation, Medical University of Lublin, Poland

Acute promyelocytic leukemia (APL) is a type of acute myeloid leukemia with distinctive biological and clinical features. It is characterized by accumulation of leukemia blasts blocked at the promyelocyte stage of differentiation [1]. The karyotype hallmark of the disease is a balanced reciprocal translocation between chromosomes 15 and 17 [2]. It gives rise to PML-RARA fusion proteins, which in addition to a differentiation block, confers major self-renewal and growth properties on the leukemic clone [1].

RARA is a member of retinoic acid (RA) nuclear receptor family. It binds DNA what yields transcriptional repression in the absence of RA ligand, but it yields activation of transcription in its presence [3]. PML belongs to ubiquitin ligases family and has ability to nucleate PML nuclear bodies, discrete structures that that recruit large number of simulated proteins [4]. These structures have been implicated, among the others, in stress response and apoptosis [3].

The prognosis for APL patients have changed markedly within the last decades. APL was lethal twenty years ago, but now is the example of leukemia with very good prognosis. The fact was caused by introduction of new drugs targeted the function of PML–RARA being the basis of pathogenesis of the disease. Thus, APL is a paradigm of malignant disease highly curable with targeted therapy.

The introduction of all-trans retinoic acid (ATRA) and later on arsenic trioxide (ATO) into the therapy of APL revolutionized the management and outcome of this kind of leukemia. Recently used treatment options using these agents either in combination with chemotherapy or even without cytotoxic agents has led to excellent therapeutic results [5].

Both ATRA and ATO directly target PML-RARA functions inducing to various extent promyelocyte differentiation and clinical remission of the disease. ATRA targets the RARA part of PML-RARA fusion, whereas ATO targets its PML moiety. ATRA treatment generally results only in transient remission of the disease but without chemotherapy it cannot cause definitive cure. Unlike ATRA, ATO induces limited transcriptional changes in malignant blasts. However, it is extremely efficient at eradicating malignant cells even as single agent. It is proposed that the destruction of clonogenic leukemia-inducing cells (LICs) that display an enhance self-renewal capacity may be the basis of ATO effectiveness in a treatment of APL patients. This new approach shows that targeting cancer cells with ability of self-renewal may represent a more effective goal than therapy aimed at inducing differentiation [1].

Despite the mechanism of action, there is no doubt that targeting the main pathologic change in this kind of leukemia improves the results of its treatment. Such an attitude should be the main way in the development of malignant diseases treatment because of its efficacy and reduction of side-effects in comparison to classical chemotherapy.

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***Corresponding author:** Monika Podhorecka, Department of Hematooncology and Bone marrow Transplantation, Medical University of Lublin, Poland, E-mail: monika.podhorecka@am.lublin.pl

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