Curing acute promyelocytic leukemia: no boost from immunity needed

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Received: October 17, 2025.
Accepted: October 30, 2025.
Early view: November 6, 2025.

https://doi.org/10.3324/haematol.2025.300055

Acute promyelocytic leukemia (APL) is an uncommon yet well-characterized subtype of acute myeloid leukemia (AML). However, it differs from all other subtypes in essentially every characteristic one considers. The most distinguishing feature is that the disease is highly curable with the vitamin A-related compound all-*trans* retinoic acid (ATRA) plus arsenic trioxide (ATO)-based targeted therapy which induces differentiation (ATRA and ATO) and apoptosis (ATO) of the leukemia cells leading to mature neutrophils.[1] The mechanisms by which the eradication of leukemia cells in APL is maintained long-term, after completion of ATRA and ATO leading to cure in the majority of patients, are not entirely known. Recent data suggest that the immune system plays an important role in the eradication of both leukemias and solid tumors.[2] In hematologic malignancies the strongest evidence comes from the effectiveness of allogeneic hematopoietic cell transplantation with consequent potential generation of graft-*versus*-host disease and an ensuing graft-*versus*-leukemia effect.[3] However, Esnault and colleagues have shed new light on the fundamental processes accounting for the highly curative treatment of APL with ATRA and ATO. They show that cure of APL with targeted therapy does not require immune effector cell activity.[4] If past is prologue, the introduction of other novel targeted agents may prove effective in additional diseases without obligatory participation of immune effector cells. Esnault and colleagues transplanted murine APL cells into both syngeneic *CB6F1* immunocompetent mice and profoundly immunodeficient NGS mice. The immunodeficient mice lacked B, T and NK cells so that both innate and adaptive immunity were not operative. Examination of both groups of mice showed that the time to leukemia development, leukemia infiltration of the spleen, and time to death were similar. Both groups were treated with the combination of ATRA and ATO. Subsequently, differentiation and kinetics of leukemia elimination were also similar with complete eradication of leukemia cells from the bone marrow in 7 days. Survival was similar in both groups. The investigators then addressed the question of how the senescent APL cells were eliminated if neither NK cells nor macrophages were present in the immunodeficient mice. Brisk reappearance of megakaryocytes and the phenomenon of emperipolesis were observed. Emperipolesis is a relatively recently identified process by which an intact cell survives in another cell that acts as a host, such as the megakaryocyte.[5] It has been described in a number of hematologic malignancies including myeloma, B-lineage acute lymphoblastic leukemia, and another favorable-risk acute leukemia, AML with inv(16).[6]

What can we glean from these observations? First, although a major focus of current research in the treatment of hematologic malignancies has successfully exploited the immune system with novel strategies such as chimeric antigen receptor T-cell therapy and bispecific antibodies, APL appears to be one example of a disease that may be effectively treated without facilitation by the immune system (Figure 1). ATRA and ATO each target and degrade one part of the oncogenic PML::RARα fusion transcript, ATRA targets RARα and ATO targets PML, which blocks differentiation.[7] One can surmise that with such highly specific targeted treatment as ATRA and ATO in a genetically homogeneous disease there is little need for a contribution from the immune system. Esnault and colleagues speculate that degradation of the PML::RARα fusion transcript is of sufficient potency to disable its oncogenic potential. They observed marked reappearance of megakaryocytes and their progenitors with inflow of differentiating cells. The authors acknowledge that the reason(s) that APL cells appear so sensitive to the process of emperipolesis and the contribution of megakaryocytes to long-term cure of APL remain to be deciphered. The second important lesson learned is the evident role of emperipolesis in the eradication of leukemic cells in APL.

Exciting discoveries during the past several decades have

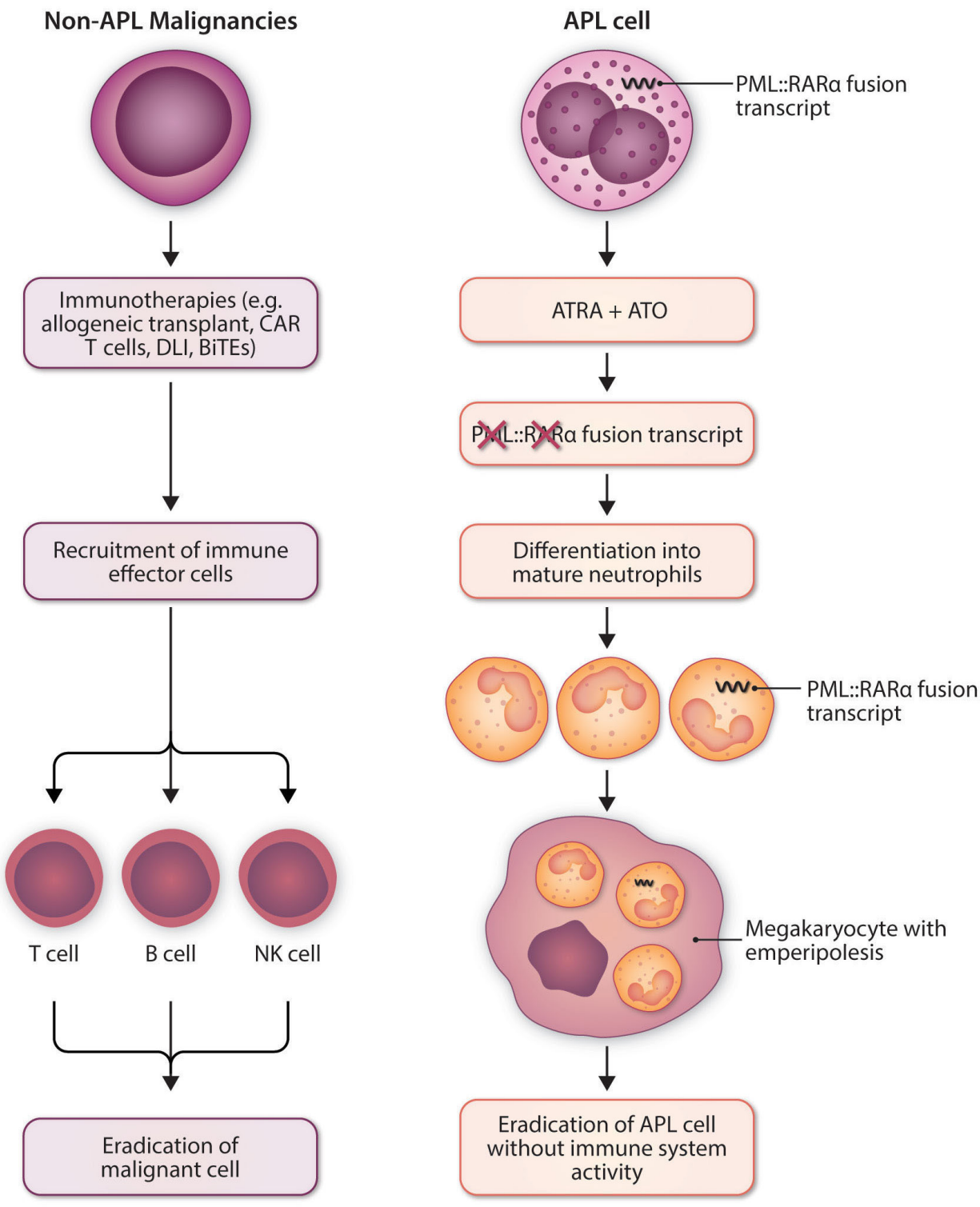

Figure 1. Potential therapeutic pathways for non-acute promyelocytic leukemia malignancies and acute promyelocytic leukemia. APL: acute promyelocytic leukemia; CAR: chimeric antigen receptor; DLI: donor lymphocyte infusion; BiTEs: bispecific T-cell engagers; ATRA: all-*trans* retinoic acid; ATO: arsenic trioxide.

identified other molecular targets to which inhibitors have been developed and are clinically effective. The third takeaway is that although it is an enticing possibility that novel targeted agents, such as IDH inhibitors, FLT3 inhibitors, and menin inhibitors, either alone or in the right combination, might be similarly effective in other hematologic malignancies without the contribution of the immune system, this will require further studies. However, APL is unique in that its pathogenesis involves a single abnormal perturbed pathway initiated by the PML::RARα fusion protein whereas the development of other forms of AML usually involves the evolution of multiple genetic changes which implies the need to target multiple genetic pathways. Interestingly, the Center for International Blood and Marrow Transplantation Research (CIBMTR) reported that among patients with APL in second complete remission autologous transplantation, with which there is no generation of a graft-*versus*-leukemia effect, results in superior overall survival.[8] This lends support to the observations of Esnault and colleagues. However, resistance to targeted agents may occur which suggests defects in innate or adaptive immunity. Therefore, strengthening the immune system or the addition of chemotherapy, as is the case in high-risk APL when anthracycline is added to ATRA and ATO, may be needed. This scenario has prompted interest in combinations of both targeted small molecule inhibitors or with cytotoxic chemotherapy in an attempt to circumvent resistance.[9] Immune-mediated therapy, for example with

chimeric antigen receptor T cells, combined with targeted small molecule inhibitors is yet another therapeutic strategy currently being explored.[10]

Disclosures

MST is a member of advisory boards for SDK Therapeutics and Moleculin Biotech and receives royalties from UpToDate.

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