Editorial

Differentiation Therapy for Myelodysplastic Syndrome

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Nearly 20 years ago in 1982, one of us wrote a review for Blood about the therapeutic potential of differentiation therapy (1). This was shortly after the initial studies with HL-60 myeloblastic leukemia cells showing that a variety of agents, including retinoids, could induce their terminal differentiation. This was followed by the finding that retinoids, especially ATRA, could cause terminal differentiation of APL cells, and this form of oral therapy has now become standard. We now know that ATRA binds to the PML-retinoic acid receptor fusion product of APL, which probably releases the co-repressors that silence a number of genes required for normal differentiation, including the transcription factor CAAT/enhancer binding protein (2). Sadly, over the last 20 years, we have learned that the abnormal cells from most MDS and AML patients rarely undergo terminal differentiation either in vitro or in vivo with “differentiation-inducing agents,” e.g., retinoids, 1,25(OH)2D3, hexamethylene bisacetamide, and IFNs have been used with limited success in patients with MDS.

A large double-blind clinical study of 13-cis retinoid acid in MDS showed several responses, but in general, the cohort receiving the retinoid had a comparable outcome as the placebo group (3). The use of ATRA as a single agent may improve hematopoiesis only in patients with 5q-syndrome. Furthermore, ATRA has been used in combination with granulocyte colony-stimulating factor and Epo or with IFNα (4–6). In some cases, complete remissions with normalization of peripheral blood cell counts and decrease of bone marrow cellularity have occurred. In vitro studies showed that 1,25(OH)2D3, the active physiologic form of vitamin D3, induced differentiation of various myeloid leukemia cell lines, including HL-60, U937, and HEL (7–9). Despite these in vitro successes, clinical studies showed limited activity (10–13). A large number of vitamin D3 analogues has been synthesized that are more potent than 1,25(OH)2D3. Although these compounds are quantitatively more active, they qualitatively have the same range of activity and, thus, may offer little benefit.

Sodium PB is an aromatic short chain fatty acid that can induce differentiation of leukemia and solid tumor cell lines (14, 15). It can activate the nuclear hormone receptor known as PPARγ, which can participate in the control of cellular proliferation and differentiation (16–19). Furthermore, it can regulate gene expression through changes in histones (20, 21). Level of expression of genes involved in cellular differentiation are regulated in part through alterations in histone conformation by histone acetylation, which is regulated through local recruitment of histone acetyltransferases and HDACs. Histone deacetylation may contribute to the transcriptional repression of genes, including tumor suppressor genes and cell cycle regulating genes; PB may reverse the deacetylation. Initial pioneer clinical results of PB in MDS by Gore et al. (22) indicated that it can be safely administered to these patients and can provide some improvement of hematopoiesis. Now, the results of an excellent study evaluating the feasibility and efficacy of prolonged exposure to continuous i.v. infusion of PB in MDS are presented by the same group (23). Only a few objective responses were achieved in a cohort of 23 individuals with both low- and high-risk MDS, as well as those with AML.

More potent HDAC inhibitors are in preclinical development. One of these promising agents is suberoylanilide hydroxamic acid, which is the prototype of a series of hydroxamic acid-based hybrid polar compounds that are potent inducers of differentiation and/or apoptosis for a variety of cancer cells, as shown by several in vitro and in vivo model systems (24).

Other agents inducing differentiation of myeloid cells are PPARγ ligands and demethylating agents. Troglitazone is a ligand for PPARγ that can partially induce differentiation of myelomonocytic leukemia cells (25) and can synergize with retinoids to inhibit proliferation of leukemic cell lines (19). It is an artificial ligand in the family known as thiazolidinediones. It is associated with liver failure and is no longer approved for use in the United States or Europe, but other family members (pioglitazone and rosiglitazone) are approved for treatment of type II diabetes. Clinical trials to evaluate the potential of these agents in MDS are ongoing; in general, these agents lack a high level of potency and will probably be of little utility.

Both 5-azacytidine and 5-aza 2′-deoxycytidine can induce differentiation of HL-60 leukemic cells (26). They lead to reduction of DNA methyltransferase activity and, therefore, can cause DNA hypomethylation (27, 28). Many genes have regions in their promoter (CpG nucleotide islands) that can be methylated, which silences expression of these genes. Theoretically, demethylation of the methylated genes, which are important in differentiation, could have clinical applications, e.g., p15INK4b, a cell cycle brake, is methylated frequently in MDS but not in normal myeloid cells (29). Initial pilot trials (30, 31) provided encouraging results that were confirmed in a multicenter study using low-dose i.v. 5-aza 2′-deoxycytidine (32). These compounds may be having their effects in MDS as either cytotoxic and/or demethylating agents.

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2 The abbreviations used are: ATRA, all-trans retinoic acid; APL, acute promyelocytic leukemia; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; 1,25(OH)2D3, 1,25-dihydroxyvitamin D3; PB, phenylbutyrate; PPAR, peroxisome proliferator activated receptor; HDAC, histone deacetylase.
At this time, we are approaching differentiation therapy similar to a blindfolded child trying to break a piñata using a blunt instrument. No rationale exists for retinoids in non-APL leukemias and MDS. Furthermore, HDAC blockers, demethylating agents, and proteasome inhibitors do not care which genes they affect. We need to remove the blindfolds to succeed efficiently.

What is the future of differentiation therapy? Can we apply what we have learned from our one major success? Retinoic acid works as a differentiation agent in APL because it is the ligand for a known genetic abnormality, the fusion gene PML-retinoic acid receptor. We need to define the aberrant pathways causing MDS and AML. Having these “road maps,” we can find ways to reverse the abnormality or stimulate the genes that are downstream of the genetic alteration. One approach to define the aberrant pathway is by gene expression profiling using microarrays. Knowing the altered pathway allows the development of a high throughput, cell-based assay system to measure the ability of a large library of small molecules to reverse the abnormality. Chemistry can then be used to synthesize related compounds permitting the development of an effective, nontoxic agent.

A cancer cell often has several aberrant, complementary pathways, including those that provide self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replicative potential, and ability to evade apoptosis, as well as the capacity for tissue invasion and sustained angiogenesis (33). Correction of any one of these abnormal pathways may either partially or completely reverse the growth advantage of the transformed cells as compared with their normal counterparts. However, the simultaneous attack of several aberrant pathways should have enhanced potency, e.g., a compound that inhibits an inappropriately expressed kinase and another agent that stimulates either the apoptotic or differentiation pathway may be much more effective than either alone. Our therapies should improve by attacking simultaneously several different abnormal pathways in the malignant cell.

References


