The Sequential Combination Paradigm in Epigenetic Therapy

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Epigenetic therapy is a novel therapeutic approach that targets DNA methylation, histone modifications or microRNAs (miRNAs). Drugs targeting DNA methylation (azacitidine and decitabine) and histone acetylation (vorinostat) are currently FDA-approved for the treatment of Myelo Dysplastic Syndromes (MDS) and cutaneous T-Cell Lymphoma (CTCL), respectively. Drugs targeting miRNAs and other histone modifications are currently in preclinical and clinical trials. A central hypothesis in epigenetic therapy is the combination of epigenetic modifiers in a specific sequential order to achieve optimal expression of epigenetically silenced tumor suppressor genes. This paradigm was established based on the observation that inhibitors of class I & II Histone Deacetylase (HDAC) enzymes cannot re-express genes silenced by promoter hypermethylation [1]. The use of a DNA Methyl Transferase (DNMT) inhibitor followed by an HDAC inhibitor is required for the re-expression of genes silenced by promoter hypermethylation. Consequently, the sequential or overlapping combination of DNA hypomethylating agents and HDAC inhibitors has been utilized in several clinical trials based on this hypothesis [2,3].

Although few previous reports did not support this hypothesis, they were considered exceptions for specific genes or for a specific class of HDAC inhibitors (SIRT1 inhibitors) [4-6]. Recently, a more comprehensive study challenged this hypothesis and demonstrated that different classes of HDAC inhibitors induce transient expression of promoter hypermethylated genes without the loss of DNA promoter hypermethylation [5]. On the other hand, DNA hypomethylating agents induced permanent and stable epigenetic reprogramming. The controversy between the recent and earlier study could be attributed to the use of insensitive method to measure gene expression, leading to failure in detecting induction of gene expression, in the earlier study.

These findings raise several questions regarding the design of clinical trials involving epigenetic modifiers. Can HDAC inhibitors induce the expression of genes silenced by promoter hypermethylation in vivo? Does the sequential design (DNMT inhibitor followed by an HDAC inhibitor) provide an advantage over the concomitant use of these agents? Does the combination of epigenetic drugs provide a clinical advantage over monotherapy? The answers to such questions would help in developing an efficient way of using these drugs and improving the outcome from epigenetic therapy.

References

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