



# Emerging Role of Hypomethylating Agents Based on Epigenetic Modifications in Relapsed Refractory Multiple Myeloma

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Epigenetics is defined as changes in genetic function without alteration of the underlying genetic code.<sup>1</sup> Dysregulation of normal epigenetic control in plasma cells is being increasingly described with effects on disease pathogenesis, drug resistance, and plasma cell (PC) plasticity. Of all epigenetic processes, DNA methylation represents a realistic target due to a significant role in pathogenesis and easy availability of hypomethylating agents in routine practice.

The best described epigenetic modification in Multiple Myeloma (MM) included promoter region methylation of tumor suppressor genes. It is now clear that the overall methylation pattern in myeloma, as with several other malignancies, is that of global DNA hypomethylation and promoter region hypermethylation of tumor suppressor genes, leading to genomic instability and disease progression. In MM, the pattern of DNA methylation varies depending on the stage at which MM cell lines are studied. In an elegant analysis, PCs from patients with MGUS, Smouldering Multiple Myeloma, and MM are shown to demonstrate a serial increase in differentially methylated loci (DMLs) with disease progression.<sup>2</sup> These modifications also have a potential prognostic role. For instance, as described by Choudhary et al,<sup>3</sup> Patterns of aberrant methylation can provide prognostic information in patients with newly diagnosed myeloma.

This mechanism has been exploited for evaluation of hypomethylating agents (HMAs) as potentially active agents in MM. As far back in 2008, azacytidine was shown to be active against MM cell lines in vitro by causing de methylation of p16, theoretically restoring its tumor suppressor function. Interestingly, exposure to azacytidine also inhibited interleukin (IL)-6 production which plays a key role in

end-organ damage mediated by plasma cells. Both these processes led to apoptosis of MM cells in vitro, indicating potential clinical utility.<sup>4</sup> Azacytidine has also been shown to have synergistic activity with several chemotherapeutic agents used in MM. For instance, bortezomib and doxorubicin have been shown to sensitize PCs in MM to the effects of azacytidine by synergistic induction of double strand DNA breaks.<sup>5</sup>

A recent phase-1 clinical study in 2020 evaluated the utility of azacytidine in combination with lenalidomide for patients with relapsed/refractory myeloma with median of five lines of therapy. It was noted that azacytidine restored the sensitivity of plasma cells to lenalidomide by reactivation of pathways controlling plasma cell differentiation. This translated into an overall response rate of 22% and progression-free survival (PFS) of 3.1 months.<sup>6</sup> Similar findings were noted by Kalf et al,<sup>7</sup> With oral azacytidine enabling a median PFS of 2.6 months in patients with lenalidomide refractory myeloma.

Identification of this novel mechanism of disease pathogenesis provides a potentially new target in MM. This pathway is especially attractive, as HMAs have been in clinical use for over a decade for acute myeloid leukemia with excellent data on toxicity and clinical use. Although several questions concerning clinical implications of plasma cell DNA methylation remain unanswered, development of further clinical data can potentially provide us a new, inexpensive treatment option for patients with MM.

## Conflict of Interest

None declared.

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