



Toward Epigenome-Based Personalized Therapeutic Strategies in Myelodysplastic Syndromes: Current Concepts and Future Landscapes

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Editorial

Myelodysplastic Syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders, characterized by impaired hematopoiesis and a propensity to progress into Acute Myeloid Leukemia (AML), leading to significant morbidity and mortality [1].

The clinical management of MDS is often difficult and for many decades it has been limited to supportive care, being a minority of patients suitable for the only curative option, such as the allogeneic Hematopoietic Stem Cell Transplantation (HSCT). The progresses made in the understanding of the complex disease pathogenesis, in which epigenetic alterations, such as aberrant DNA methylation and histone modifications, exert a key role [2,3], have allowed the introduction in the clinical practice of effective and targeted therapeutic compounds, such as Hypomethylating Agents (HMAs) [4-7]. Moreover, new treatment scenarios are opening from the results of clinical trials [8-12] and further advances are expected in the near future in the clinical practice [1,13].

Epigenetic regulators, including TET2, DNMT3A and EZH2, are often mutated in MDS patients. The most extensively investigated HMAs are two nucleoside analogues, such as azacitidine and decitabine [4,6,7]; these HMAs have represented a major breakthrough treatment in the setting of MDS and related disorders. Indeed, they have been a major focus of clinical research over the last decade, becoming the standard of care of high risk MDS [1,12-14], high risk Chronic Myelomonocytic Leukemia (CMML) MDS subtype [15-17] and hypoproliferative forms of AML whenever unsuitable for Intensive Chemotherapy (ICT) [18,19]. HMAs are defined so given their property to induce DNA hypomethylation, including that of several promoter tumor suppressor genes. As a matter of fact as result of acquired (epigenetic) modifications, some critical tumor suppressor genes may be hypermethylated and, therefore, repressed.

Hypermethylation consists in the insertion of CH₃ groups to the Cytosine preceding Guanosine (CpG) in specific sites of DNA, such as CpG islands located in the promoter of tumor-associated genes, which, under normal conditions, are unmethylated. Their aberrant methylation causes the inactivation of the promoter and consequently the inhibition of gene transcription (gene silencing) [20,21]. This process is catalyzed by DNA Methyltransferases (DNMTs), of which several isoforms are known; however, three of them (DNMT1, 3A and 3B) are enzymatically active. The silencing of tumor-suppressor genes by aberrant methylation has been recognized as a major determinant in the pathogenesis of many cancers and, in particular, MDS and MDS-related myeloid neoplasm [20,21].

Hypermethylation is a reversible process and, as such, it can be used as a target. The reversal of aberrant methylation and the re-expression of silenced tumor suppressor genes can be induced by the inhibition of DNMTs. These understandings provided the rationale supporting the use of HMAs as DNMTs inhibitors in the clinical practice, based on the evidences suggesting that they may reverse epigenetic gene silencing at specific genomic targets. Undeniably, in such settings, these agents have demonstrated to improve both survival [14,22,23] and Quality of Life (QoL) [24], representing also a suitable therapeutic approach for frail and elderly patients [13,25]. Moreover, in the difficult setting of therapy-related myeloid neoplasms, including MDS which are usually associated to clinical and biologic unfavorable prognostic features, such as high levels of DNA methylation, favorable results with a 42% of overall response by azacitidine have been reported [26]. In addition, in patients with Ph-negative myeloproliferative neoplasms progressing into blast phase, the efficacy and safety of azacitidine with possible achievement of long-lasting responses in a significant proportion of them have been also described [27]. Finally, pre-treatment of higher-risk MDS with azacitidine as bridge

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to HSCT is feasible and can be another suitable option in higher-risk MDS [28].

Unfortunately, although HMAs used as first line agents induce responses in up to 40% of MDS patients, most patients ultimately experience loss of response [10,26] followed usually by a rapid dismal outcome [10,29,30].

Potential therapies after HMA failure are under development and include guadecitabine, a newer HMA less susceptible to in-vivo deamination, monoclonal antibodies targeting immune checkpoints, such as pembrolizumab, nivolumab, ipilimumab, as well as agents targeting the inhibition of multiple kinases (rigosertib), BCL2 (venetoclax) and others [10].

In conclusion, the study of epigenetic mechanisms involved in the development of MDS and MDS-related hematologic malignancies have recently provided the rationale for the application of innovative therapeutic options in this group of patients. For many years only a very small subgroup of patient had access to the few treatments available such as HDC and ICT, while the vast majority could be granted to supportive treatments only. Very promising results have been obtained and are now achieved in patients treated with HMA both in terms of objective responses with rescue of an effective hemopoiesis, and QoL.

A comprehensive review of the epigenetic regulatory mechanisms in MDS is presented by et al. in this number of American Journal of Leukemia Research. The progresses in understanding the biological processes combined with the development of novel epigenetic therapies and their clinical use will expand this comprehensive knowledge platform allowing personalizing the management of MDS patients in a future ready to come.

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