American Journal of Leukemia Research

Editorial
Published: 01 Sep, 2018

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 azacytidine 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 CH_3 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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Received Date: *05 Mar 2018*
Accepted Date: *25 Aug 2018*
Published Date: *01 Sep 2018*

Citation:
Abruzzese E, Niscola P. Toward Epigenome-Based Personalized Therapeutic Strategies in Myelodysplastic Syndromes: Current Concepts and Future Landscapes. Am J Leuk Res. 2018; 2(2): 1012.

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.

References

1. Montalban-Bravo G, Garcia-Manero G. Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management. Am J Hematol. 2018;93(1):129-47.
2. Dussiau C, Fontenay M. Mechanisms underlying the heterogeneity of myelodysplastic syndromes. Exp Hematol. 2018;58:17-26.
3. Issa JP. The myelodysplastic syndrome as a prototypical epigenetic disease. Blood. 2013;121(19):3811-7.
4. Li KK, Luo LF, Shen Y, Xu J, Chen Z, Chen SJ. DNA methyltransferases in hematologic malignancies. Semin Hematol. 2013;50(1):48-60.
5. Bell JA, Galaznik A, Huelin R, Stokes M, Guo Y, Fram RJ, et al. Systematic Literature Review of Treatment Options and Clinical Outcomes for Patients With Higher-Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia. Clin Lymphoma Myeloma Leuk. 2018;18(4):e157-e66.
6. Shapiro RM, Lazo-Langner A. Systematic review of azacitidine regimens in myelodysplastic syndrome and acute myeloid leukemia. BMC Hematol. 2018;18:3.
7. Yun S, Vincelette ND, Abraham I, Robertson KD, Fernandez-Zapico ME, Patnaik MM. Targeting epigenetic pathways in acute myeloid leukemia and myelodysplastic syndrome: a systematic review of hypomethylating agents trials. Clin Epigenetics. 2016;8:68.
8. Yang H, Bueso-Ramos C, DiNardo C, Estecio MR, Davanlou M, Geng QR, et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. Leukemia. 2014;28(6):1280-8.
9. Ørskov AD, Treppendahl MB, Skovbo A, Holm MS, Friis LS, Hokland M, et al. Hypomethylation and up-regulation of PD-1 in T cells by azacytidine in MDS/AML patients: A rationale for combined targeting of PD-1 and DNA methylation. Oncotarget. 2015;6(11):9612-26.
10. Montalban-Bravo G, Garcia-Manero G, Jabbour E. Therapeutic choices after hypomethylating agent resistance for myelodysplastic syndromes. Curr Opin Hematol. 2018;25(2):146-53.
11. Kharfan-Dabaja MA. Guadecitabine for AML and MDS: hype or hope? Lancet Oncol. 2015;16(9):1009-11.
12. Voso MT, Lo-Coco F, Fianchi L. Epigenetic therapy of myelodysplastic syndromes and acute myeloid leukemia. Curr Opin Oncol. 2015;27(6):532-9.
13. Luskin MR, Abel GA. Management of older adults with myelodysplastic syndromes (MDS). J Geriatr Oncol. 2017;9(4):302-7.
14. Voso MT, Niscola P, Piciocchi A, Fianchi L, Maurillo L, Musto P, et al. Standard dose and prolonged administration of azacitidine are associated with improved efficacy in a real-world group of patients with myelodysplastic syndrome or low blast count acute myeloid leukemia. Eur J Haematol. 2016;96(4):344-51.
15. Breccia M, Voso MT, Alimena G. Chronic myelomonocytic leukemia treatment with azacitidine: what have we learned so far? Leuk Res. 2013;37(2):204-5.
16. Niscola P, Tendas A, Abruzzese E, Caravita T, Cupelli L, Giovannini M, et al. Advanced chronic myelomonocytic leukemia in elderly and frail patients managed by azacitidine in the field of clinical practice. Ann Hematol. 2017;96(9):1591-3.
17. Solary E, Itzykson R. How I treat chronic myelomonocytic leukemia. Blood. 2017;130(2):126-36.
18. Ramos F, Thépot S, Pleyer L, Maurillo L, Itzykson R, Bargay J, et al. Azacitidine frontline therapy for unfit acute myeloid leukemia patients: clinical use and outcome prediction. Leuk Res. 2015;39(3):296-306.
19. De Bellis E, Fianchi L, Buccisano F, Criscuolo M, Maurillo L, Cicconi L, et al. Treatment of Low-Blast Count AML using Hypomethylating Agents. Mediterr J Hematol Infect Dis. 2017;9(1):e2017045.
20. Herman JG, Baylin SB. Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med. 2003;349(21):2042-54.
21. Takahashi S. Epigenetic aberrations in myeloid malignancies (Review). Int J Mol Med. 2013;32(3):532-8.
22. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223-32.
23. Breccia M, Voso MT, Maurillo L, Niscola P, Fianchi L, Aloe Spiriti MA, et al. Real-life experience with azacitidine in myelodysplastic syndromes according to IPSS cytogenetic profile. Am J Hematol. 2014;89(5):565.
24. Kornblith AB, Herndon JE, Silverman LR, Demakos EP, Odchimar-Reissig R, Holland JF, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol. 2002;20(10):2441-52.
25. Niscola P, Palombi M, Trawinska MM, Tendas A, Giovannini M, Scaramucci L, et al. Managing myelodysplastic syndromes in very old patients: a teaching case report. Clin Interv Aging. 2013;8:391-4.
26. Fianchi L, Criscuolo M, Lunghi M, Gaidano G, Breccia M, Levis A, et al. Outcome of therapy-related myeloid neoplasms treated with azacitidine. J Hematol Oncol. 2012;5:44.
27. Andriani A, Montanaro M, Voso MT, Villivà N, Ciccone F, Andrizzi C, et al. Azacytidine for the treatment of retrospective analysis from the Gruppo Laziale for the study of Ph-negative MPN. Leuk Res. 2015;39(8):801-4.
28. Voso MT, Leone G, Piciocchi A, Fianchi L, Santarone S, Candoni A, et al.

Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study. Ann Oncol. 2017;28(7):1547-53.

29. Santini V. Life after hypomethylating agents in myelodysplastic syndrome: new strategies. Curr Opin Hematol. 2015;22(2):155-62.

30. Niscola P, Tendas A, Cupelli L, Giovannini M, Piccioni D, Scaramucci L, et al. Dismal outcome of acute myeloid leukemia secondary to myelodysplastic syndrome and chronic myelomonocytic leukemia after azacitidine failure in a daily-life setting. Acta Haematol. 2015;133(1):64-6.