Seminars in Hematology 54 (2017) 147–153

Contents lists available at ScienceDirect

Seminars in Hematology

journal homepage: www.elsevier.com/locate/enganabound

Optimizing the use of hypomethylating agents in myelodysplastic syndromes: Selecting the candidate, predicting the response, and enhancing the activity

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ARTICLE INFO

Keywords:
Azacitidine
Decitabine
Myelodysplastic syndromes
Response prediction
Combination therapy
Molecular

ABSTRACT

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders that have a substantial impact on patients' quality of life, in addition to causing significant morbidity and mortality. The hypomethylating agents (HMAs) azacitidine and decitabine are approved for use in the United States and in Europe for the treatment of MDS or acute myeloid leukemia (AML) and, in the case of azacitidine, prolong survival in higher-risk patients. Neither is curative, though, and given the lack of clear treatment guidelines after HMA treatment failure, it is imperative to optimize patient selection and identify the right timing of HMA treatment initiation and response evaluation to maximize patient benefit. Initiatives to improve outcomes have focused on HMA-based drug combinations to enhance HMA activity or treat MDS using complementary drug mechanisms of action. In this review, we will summarize the available data to aid decision-making while treating MDS patients with HMAs.

1. Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders that affect a predominantly older population, with a median age of 71 years at diagnosis and an incidence rate of 4.9 per 100,000 [1–3]. The only potentially curative treatment option is hematopoietic cell transplantation. The majority of patients do not undergo transplant due to factors such as patient preference, medical comorbidities that raise transplant risks to unacceptable levels, and lack of adequately matched donors. Given the recognized heterogeneity of subtypes within MDS, treatment is classically guided by the patients' symptoms, type and number of affected cell lines, and the disease risk of transformation to acute myeloid leukemia (AML). The World Health Organization classification was recently updated in 2016 with more emphasis on the number of affected cell lines or number of cytopenias rather than on marrow dysplasia [4]. Despite the existence of many classification systems for MDS risk assessment, the International Prognostic Scoring System (IPSS) and revised-IPSS (IPSS-R) continue to be the most widely used worldwide [5,6]. Pragmatically, patients are classified into lower- or higher-risk MDS based on having IPSS/IPSS-R scores of $< 1.5/\leq 3.5$, or $\geq 1.5/> 3.5$, respectively. The majority of patients fall into the lower-risk category, with infectious risk secondary to neutropenia being the most common cause of death [7].

The hypomethylating agents (HMAs) azacitidine and decitabine are DNA methyl-transferase enzyme inhibitors and are approved by the US Food and Drug Administration (FDA) for treatment of all subtypes of MDS. In the European Union, azacitidine is approved for treatment of higher-risk MDS, while decitabine is approved for the treatment of AML. Azacitidine and its deoxy counterpart, decitabine, act by reversing DNA methylation by inhibiting the enzyme DNA methyltransferase (DNMT1). This leads to DNA de-methylation of the cytosine residues allowing chromatin de-coiling and expression/transcription of tumor-suppressor genes. We will focus the scope of our discussion on optimizing the use of these HMAs, summarizing the data and landmark trials in both lower- and higher-risk disease groups.

2. Indications of HMA Therapy

2.1. Lower-risk MDS

No prospective trial has ever demonstrated that a drug can provide a survival advantage in lower-risk MDS patients.

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[1] M.A. Sekeres receives funding support from the Edward P. Evans Foundation and the Dresner Foundation.

http://dx.doi.org/10.1053/j.seminhematol.2017.06.001
0037-1963/$/

Consequently, the goals of treatment are to reduce patient morbidity by preventing, minimizing, or eliminating transfusion requirements and to improve quality of life. As the dominant cytopenia in lower-risk MDS is anemia, achieving transfusion independence is an important therapeutic goal for these patients, and is most frequently attempted with the use of erythropoiesis-stimulating agents (ESAs) or with lenalidomide (most effectively in patients with the del(5q) cytogenetic abnormality). While HMAs can also improve anemia in patients with lower-risk MDS, they are not often used as first-line therapy for patients when the sole cytopenia is anemia [8].

The response rate for HMA therapy is 30%–40%, using the International Working Group (IWG) response criteria [9,10]. In non-del(5q) MDS, HMA treatment can be considered second-line treatment in patients who fail to respond to first-line ESAs, ie, those who are primary refractory or who relapse/lose response within 6 months of ESA therapy. These patients have a higher risk of progression to AML and unfavorable survival outcomes. The 5-year AML transformation rate was estimated at 20.3% with an overall survival rate of 36.5% in these patients [11,12]. A recent randomized phase II trial by Thepot et al demonstrated diminished benefit to azacitidine, with an overall response rate (ORR) of 25%–35% and no added benefit of continuing treatment with epoietin-beta combined with azacitidine. However, mutations in the *SF3B1* gene were associated with improved erythroid response rates (ORR 49%) in that trial [13].

Patients with del(5q) receive first- or second-line (following ESA) therapy with lenalidomide, and the transfusion independence response rate is 60%–70% [14]. At relapse or loss of response to lenalidomide, HMAs remain effective as subsequent-line treatment and demonstrated comparable response rates (ORR 50%) in a small population of 36 patients after lenalidomide treatment failure [15]. The median overall survival after loss of response to lenalidomide was 31 months in a study by Prebet et al, demonstrating a survival advantage for patients treated with HMAs post lenalidomide failure versus best supportive care (overall survival 31 ν 14 months, respectively, $P = .003$) [16].

In non-del(5q) patients who lose response to ESA, HMA treatment showed no significant difference in erythroid-hematologic improvement (HI-E) when used as second-line (following ESA) or third-line (following ESA and lenalidomide) with HI-E of 39% versus 30%, respectively ($P = .2$). However, these results were improved for lenalidomide, achieving HI-E of 20% versus 11% ($P = .046$) when used in second-line (post ESA) versus third-line (post ESA and HMA) settings, respectively. In the case of lenalidomide, used in second- versus third-line settings, the survival advantage did not reach statistical significance, with median overall survival times of 79 months versus 61 months, respectively ($P = .4$). However, the rate of AML transformation was higher when lenalidomide was used in the third-line setting (9% ν 22%, $P = .03$). It is therefore recommended to use lenalidomide first prior to HMA therapy in non-del(5q) patients [17].

Patients with isolated thrombocytopenia represent approximately 6% of all MDS diagnoses [8]; however, the total incidence of thrombocytopenia in MDS patients with bi- or pan-cytopenia is much higher, occurring in up to 67% of patients [18]. HMAs can achieve platelet responses in 35%–40% of lower-risk MDS patients, and thus remain a viable alternative to, for example, thrombopoietin agonists [19] in patients presenting with only severe thrombocytopenia (platelet count $< 30 \times 10^9$/L) [8].

The more common indication for HMA therapy in lower-risk MDS patients, however, is in those with multilineage dysplasia or hypocellular marrows, and consequent pancytopenia. Patients > 65 years of age without disease characteristic predictors of response to immunosuppressive therapy with anti-thymocyte globulin/cyclosporine (these include a hypoplastic marrows, HLA-DR15, normal karyotype, and absence of bone marrow blasts) should be considered for upfront treatment with HMAs, particularly if manifesting with sequelae to thrombocytopenia (platelet count $< 30 \times 10^9$/L) or are having recurrent infections due to neutropenia [20]. Patient factors associated with higher mortality rates include older age, male gender, and poor-risk karyotype [21]. Therefore, it is key to closely monitor these patients throughout the period of HMA therapy as cytopenias can worsen initially and responses are often delayed, with best response reached after four to six cycles. An initial report of an ongoing trial conducted through the MDS Clinical Research Consortium using “low-dose” HMAs in patients with lower-risk MDS showed an ORR of 61% as compared to conventional dosing of the HMAs (azacitidine 75 mg/m^2 subcutaneously/intravenously [IV] for 7 days or decitabine 20 mg/m^2 IV for 5 days every 28-day cycle) [22,23].

2.2. Higher-risk MDS

Higher-risk MDS are treated more aggressively at diagnosis, regardless of peripheral blood counts, given the increased risk of transformation to AML in these patients and poor overall survival (5,6). Higher-risk MDS patients have a median overall survival of < 2 years, and a discussion of bone marrow transplantation should be initiated at diagnosis [24]. The standard, frontline therapy for higher-risk MDS patients is a HMA, be it azacitidine or decitabine. Azacitidine was shown to improve overall survival in patients with higher-risk MDS in a phase III trial, AZA001. Patients were randomized to receive azacitidine (75 mg/m^2) daily for 7 days out of a 28-day cycle or best supportive care, low-dose cytarabine, or intensive “7+3” chemotherapy. The median overall survival was increased by 9.5 months in the azacitidine arm (overall survival 24.5 months for azacitidine ν 15.0 months for conventional care arm) (hazard ratio [HR] 0.58, $P = .0001$) [25].

Decitabine was also studied in a phase III trial in older patients with intermediate- or high-risk MDS, in which patients were randomized to receive decitabine or best supportive care. The median overall survival was improved by 1.6 months for those receiving decitabine, which was not a significant benefit (10.1 months for decitabine ν 8.5 months for best supportive care arm; HR 0.88, $P = .38$) [26]. Reasons postulated for the difference in outcomes between the two randomized studies include different durations of therapy, longer for patients on the AZA-001 study; and profoundly different patient populations enrolled to the trials, with those on the decitabine study likely having MDS for a longer duration of time prior to being treated, given the extreme discordance in median survival between the control arms (15.1 months on AZA001, 8.5 months for the decitabine study).

HMAs are recommended to be used for a minimum of 6 months before assessing response/failure of treatment to maximize the potential for benefit, as 90% of patients destined to respond to these therapies do so within that time period. After failure of hypomethylating therapy, patients have dismal outcomes, with a median survival of 4–6 months, and treatment options are limited [27,28]. As a result, this population has become a new regulatory frontier, with abundant options to enroll patients on clinical trials to better establish new standards of care. Of note, certain somatic mutations were found to be more enriched in this patient population (compared to mutations found in lower-risk MDS), including *TP53, GATA2, KRAS, RUNX1, STAG2, ASXL1, ZRSR2,* and *TET2* mutations [29].

3. Predicting response to HMAs

Approximately one third of MDS patients respond to HMAs. While it is still unclear why the response rates to HMAs are so low,