

## Treatment Options for Myelodysplastic Syndromes

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### Abstract

Myelodysplastic syndromes (MDS) are a group of heterogeneous hematopoietic stem cell disorders characterized by peripheral blood cytopenias and a risk of transformation to acute myeloid leukaemia. Until recently, treatment of MDS predominately consisted of supportive care measures. However, three agents for the treatment of MDS have recently been approved: lenalidomide, decitabine, and azacitidine. These agents have dramatically improved the outcomes for patients with MDS. To date, azacitidine is the only agent that has demonstrated a survival advantage when compared with conventional care. Novel agents and combination regimens including lenalidomide, decitabine and azacitidine are being explored in an effort to further improve patient outcomes.

### Keywords

Myelodysplastic syndromes, MDS, azacitidine, decitabine, lenalidomide, hypomethylating agents, supportive care, immunosuppressive therapy

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Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders that impair normal hematopoiesis, resulting in a variable number of cytopenias and a potential to evolve into acute myeloid leukaemia (AML).<sup>1</sup> With a median age at diagnosis around 70 years, MDS typically affects the elderly.<sup>1,2</sup> Hence, there is much morbidity and mortality associated with this patient population, as patients frequently suffer from complications due to cytopenias as well as other comorbidities. The two systems used for classifying MDS are the French American and British (FAB) criteria and the more recently revised World Health Organization (WHO) classification system. A third system, the International Prognostic Scoring System (IPSS), can predict survival based on percentage of bone marrow blasts, karyotype and number of peripheral blood cytopenias<sup>3</sup> and is the most widely used prognostic tool for assisting with treatment decisions.

For many years, supportive care with blood products (red blood cell [RBC] and platelet transfusions), hematopoietic growth factors and antibiotics remained the only treatment modality for MDS patients, until the development of three novel agents that may alter the natural history of this disease. Within the past decade, the US Food and Drug Administration (FDA) has approved an immunomodulatory agent, lenalidomide (Revlimid™, Celgene) and two hypomethylating agents, decitabine (Dacogen™, Eisai, Inc.) and azacitidine (Vidaza™, Celgene) for the treatment of patients with MDS. In simple practice, therapy is tailored to IPSS score with an emphasis on supportive care therapies or lenalidomide for lower-risk patients (IPSS low or intermediate [int]-1) and more intensive therapies such as conventional chemotherapy, allogeneic hematopoietic stem cell transplant (HST) and clinical trials,

as well as hypomethylating agents, for patients with higher-risk disease (IPSS int-2 or high) or lower-risk patients with progressive disease.<sup>3</sup>

### Treatment of Lower-risk Myelodysplastic Syndromes Supportive Care

Initial clinical management of lower-risk MDS patients with symptomatic anemia includes the use of erythropoiesis stimulating agents (ESAs), such as epoetin alpha (Epogen™, Amgen; Procrit™, Ortho Biotech) or darbepoetin alpha (Aranesp™, Amgen). ESAs have been shown to reduce RBC transfusion needs in MDS patients and when given with granulocyte colony-stimulating factor (G-CSF), ESAs have been shown to confer a survival advantage.<sup>4</sup> The likelihood of response to ESAs has been correlated with RBC transfusion needs and serum erythropoietin (EPO) levels. Patients with low transfusion requirements (<two units packed red blood cells [pRBC] per month) and with baseline serum EPO level ≤500 mU/ml are predicted to have a good response to ESAs and G-CSF, whereas patients with higher transfusion needs (≥two units pRBC per month) and serum EPO levels >500 mU/ml are least likely to respond to ESAs.<sup>5,6</sup> Demonstrated in a recent prospective, randomised study by the Eastern Cooperative Oncology Group (ECOG), patients with low-risk MDS and low serum EPO levels experienced higher erythroid response rates when given ESAs with or without G-CSF compared with patients with high-risk disease.<sup>7</sup>

### Immunosuppressive Therapy

A subset of MDS patients with bone marrow failure responds to immunosuppressive therapy (IST), which suggests that an immune-

mediated pathogenesis is responsible for the cytopenias. In patients with hypocellular bone marrow, IST with antithymocyte globulin (ATG), cyclosporine or both can be utilised. In patients with MDS, ATG alone has been shown to decrease RBC transfusion requirements as well as improve neutropenia and thrombocytopenia.<sup>8</sup> Likewise, long-term outcomes in low-risk MDS patients have shown higher response rates with ATG and cyclosporine (54 %) than ATG alone (29 %) ( $p=0.004$ ).<sup>9</sup> Factors that have been shown to favour response to ATG include age,<sup>8-10</sup> human leukocyte antigen (HLA)-DR15 positivity<sup>8-10</sup> and shorter duration of RBC transfusion requirements.<sup>8,9</sup> In general, patients will respond to IST within three to four months and will remain clinically stable for years, but many eventually relapse with return of cytopenias. Recently, a Phase I/II pilot study demonstrated alemtuzumab, an anti-CD52 monoclonal antibody, produces durable responses in patients with intermediate-risk MDS who fit criteria to respond to IST. Ninety-seven per cent of int-1-risk patients and 57 % of int-2 patients responded to alemtuzumab by three months, which was superior to response rates reported with ATG alone.<sup>9</sup> Furthermore, at 12 months follow-up, 56 % of responding patients had normal blood counts and 78 % of patients were transfusion independent.<sup>11</sup>

## Immunomodulating Therapy—Lenalidomide

Lenalidomide was FDA approved in 2005 for the treatment of patients with transfusion-dependent anaemia due to low- and int-1-risk MDS associated with deletion 5q karyotype [del(5q)]. The approval of lenalidomide was based on two Phase II studies demonstrating a high frequency of erythroid responses in patients with an isolated del(5q) or del(5q) with other abnormalities.<sup>12,13</sup> The majority of patients in these studies were IPSS low- or int-1-risk patients with transfusion-dependent anemia. The majority of patients achieved a hematologic response (reduced transfusion needs) and became transfusion independent. Of note, responses occurred despite karyotype complexity and patients with thrombocytopenia at baseline were less likely to respond to lenalidomide compared with patients with platelets  $>100,000/\text{ml}$  at baseline. Furthermore, a majority of patients had cytogenetic improvement and 45 % had a complete cytogenetic response. Hence, these responses illustrate the effect of lenalidomide on the biology of the disease by reversing the cytogenetic abnormalities associated with the 5q13 deletion.<sup>13</sup> Following these studies, Raza et al. evaluated the safety and efficacy of lenalidomide in 214 patients with transfusion-dependent anemia due to lower-risk MDS without del(5q). Hematologic responses were lower than those observed in patients with del(5q), but the rate of transfusion independence was 26 % and the median duration of transfusion independence was 41 weeks.<sup>14</sup> Lenalidomide demonstrated a potential benefit for low-risk patients without del(5q) who remain transfusion dependent after supportive care measures or for patients who are not candidates for ESAs or more intensive therapy. Although lenalidomide is generally well tolerated, it induces significant cytopenias resulting in dose reduction or interruption in a majority of patients.

## Treatment of Higher-risk Myelodysplastic Syndromes

### Hypomethylating Agents

#### Azacitidine and Decitabine

Azacitidine and decitabine are both hypomethylating agents that irreversibly inhibit DNA methyltransferase, resulting in progressive loss of methylation and reactivation of tumour suppressor genes. Azacitidine was the first DNA methyltransferase inhibitor approved by the FDA in

2004, for the treatment of all FAB subtypes of MDS. This approval was based on the results of three Cancer and leukemia group B (CALGB) studies that evaluated the efficacy and safety of azacitidine 75 mg/m<sup>2</sup> intravenous (IV) or subcutaneous (SQ) x seven days every 28 days in MDS patients. A pooled analysis of the CALGB trials (8421, 8921 and 9221) reported overall response rates (ORR) between 40 and 47 % (complete remission (CR) 10–17 %, partial remission (PR) 1 %, hematological improvement (HI) 23–36 %) for azacitidine and 17 % (HI only) for best supportive care (BSC) by International Working Group (IWG) 2000 criteria.<sup>15,16</sup>

Subsequently, the AZA-001 trial established an improved overall survival in patients with higher-risk MDS. In this Phase III trial, 358 patients with IPSS int-2- or high-risk MDS were randomized to receive azacitidine (75 mg/m<sup>2</sup> SQ daily x seven days, every 28 days) or conventional care (BSC, low-dose cytarabine, or intensive chemotherapy). The overall survival was significantly longer with azacitidine compared with conventional care (24.5 versus 15 months; hazard ratio (HR): 0.58; 95 % confidence interval (CI): 0.43–0.77;  $p=0.0001$ ) and was present regardless of MDS subtype and IPSS subgroup. The median time to AML transformation was improved with azacitidine compared with conventional care (17.8 versus 11.5 months; HR: 0.5; 95 % CI: 0.35–0.7;  $p<0.0001$ ). By IWG criteria,<sup>15</sup> azacitidine-treated patients demonstrated higher response rates.<sup>17</sup>

In 2006, decitabine was also approved for the treatment of all FAB subtypes of MDS. This approval was based on the results of a Phase III multicenter trial that randomized 170 MDS patients to treatment with decitabine at 15 mg/m<sup>2</sup> IV over three hours every eight hours for three consecutive days every six weeks (135 mg/m<sup>2</sup>/course) or to BSC.<sup>18</sup> More than half of the patients had higher-risk MDS. By IWG criteria,<sup>15</sup> the ORR for the decitabine arm was 30 % (CR 9 %, PR 8 %, HI 13 %) compared with 7 % (CR 0 %, PR 0 %, HI 7 %) with BSC ( $p<0.001$ ). Although there was a trend for improved time to AML progression or death in patients treated with decitabine (12.1 versus 7.6 months,  $p=0.16$ ), it was only significant when analyzing the subgroup with IPSS int-2- or high-risk disease (12.3 versus 7.3 months,  $p=0.03$ ). There was no difference in overall survival between the two groups.<sup>18</sup> The European Organization for Research and Treatment of Cancer (EORTC) and the German MDS Study Group conducted a similar Phase III study, using the same dose of decitabine.<sup>19</sup> This trial randomized 233 elderly patients with higher-risk MDS to either decitabine or BSC and confirmed similar response rates with an ORR, by IWG criteria,<sup>15</sup> of 34 % (CR 13 %, PR 6 %, HI 15 %) with decitabine compared with 2 % (HI only) with BSC. Despite an improvement in progression-free survival with decitabine, there was no difference in overall survival or time to AML between the two groups. A median of four cycles were given; however, 40 % of patients received no more than two cycles.<sup>19</sup>

Interested in optimizing the hypomethylation properties of decitabine, a lower dose of decitabine (100 mg/m<sup>2</sup>/course) was subsequently evaluated at the MD Anderson Cancer Center (MDACC) in a Phase II trial that compared three different schedules of decitabine: 10 mg/m<sup>2</sup> IV over one hour daily for 10 days, 20 mg/m<sup>2</sup> IV over one hour daily for five days or 20 mg/m<sup>2</sup> SQ daily for five days every four weeks.<sup>20</sup> The ORR by modified IWG criteria<sup>21</sup> was 73 % (CR 34 %, PR 1 %, marrow CR [mCR] 24 % and HI

14 %) and the 20 mg/m<sup>2</sup> IV x five days schedule produced the best clinical responses with a reported CR rate of 39 %. The median number of cycles given was nine, with a median of three cycles to achieve response.<sup>20</sup> The activity of the decitabine five-day IV schedule was confirmed by the Alternative dosing for outpatient treatment (ADOPT) study.<sup>22</sup> In this multicenter trial, 99 patients with MDS were treated with decitabine 20 mg/m<sup>2</sup> IV x five days every four weeks. By modified IWG criteria,<sup>21</sup> the ORR was 51 % and the median survival was 19.4 months. Patients received a median of five cycles of treatment and 82 % of the responses were seen by the second cycle.<sup>22</sup> Furthermore, the efficacies of low-dose decitabine and intensive chemotherapy were compared in a historic comparison of patients with higher-risk MDS at the MDACC. This study showed a similar CR rate, but significantly lower six-week and three-month mortality rates and improved survival with decitabine.<sup>23</sup>

Patients require several courses of azacitidine and decitabine (three to six cycles) before demonstrating a response, so drug- and disease-induced myelosuppression can be common during this time period. Therefore, treatment should continue with both agents for a minimum of three to four cycles before declaring therapy a failure. Although azacitidine is an outpatient regimen, it is complicated by a seven-consecutive-day regimen, necessitating weekend administration. More convenient regimens (i.e. five-day, five days followed by two additional weekdays) have been explored in predominately lower-risk patients and response rates appear similar among the three regimens.<sup>24,25</sup> However, it is not certain that these regimens will lead to a survival advantage in higher-risk MDS patients.

### Stem Cell Transplant

The only potential curative option for MDS is allogeneic hematopoietic stem cell transplant (HSCT), but it is restricted to patients with a donor and those free from co-morbidities that may preclude them from this option.

For patients older than 55 years, the mortality rate is approximately 38 %. For patients who are eligible for HSCT, the timing of transplantation is important. Published data identifying the optimal timing of HSCT is scant. However, a retrospective analysis of patients younger than 60 years of age who received a myeloablative conditioning regimen from a sibling donor transplant suggests that survival is better for low- and int-1-risk patients receiving a transplant at the time of disease progression rather than at diagnosis. Outcomes for int-2- and high-risk patients are better when transplantation is performed as early as possible.<sup>26</sup> Therefore, donor screening for younger patients should begin as soon as possible regardless of the IPSS score at diagnosis. This sheds some light on the timing for younger patients. For elderly patients, reduced-intensity transplants may be an option.

### Conclusion

Patients with MDS are predominately elderly and have multiple comorbidities that preclude them from curative therapies. For many years, supportive care measures remained the only treatment modality for MDS patients, until the development of three novel agents that may alter the biology of this disease. The recent development of three FDA-approved agents, lenalidomide, azacitidine and decitabine, has dramatically changed the MDS landscape. Lenalidomide is remarkably effective in lower-risk patients, producing complete transfusion independence in the majority of del(5q) and some non-del(5q) patients. The hypomethylating agents azacitidine and decitabine are effective in the setting of higher-risk MDS patients, producing responses in nearly half of treated patients. Compared with conventional care regimens, azacitidine has significantly improved the median survival of higher-risk patients. Despite these therapeutic advances, the responses in higher-risk patients are not durable, making the search for other novel agents necessary. ■

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