



## Guidelines

# Part 5: Myelodysplastic syndromes—Treatment of high-risk disease



Silvia Maria Meira Magalhães<sup>a,\*</sup>, Maria de Lourdes Lopes Ferrari Chauffaille<sup>b,c</sup>,  
Elvira Deolinda Rodrigues Pereira Velloso<sup>d,e</sup>, Renata Buzzini<sup>f</sup>,  
Wanderley Marques Bernardo<sup>d,f</sup>

<sup>a</sup> Hospital Universitário Walter Cantídio, Universidade Federal do Ceará (HUWC UFC), Fortaleza, CE, Brazil

<sup>b</sup> Escola Paulista De Medicina da Universidade Federal de São Paulo (EPM Unifesp), São Paulo, SP, Brazil

<sup>c</sup> Grupo Fleury, São Paulo, SP, Brazil

<sup>d</sup> Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC FMUSP), São Paulo, SP, Brazil

<sup>e</sup> Hospital Israelita Albert Einstein, São Paulo, SP, Brazil

<sup>f</sup> Associação Médica Brasileira (AMB), São Paulo, SP, Brazil

## ARTICLE INFO

### Article history:

Received 22 May 2018

Accepted 22 May 2018

Available online 27 July 2018

**Objective:** The objective of these guidelines is to evaluate existing treatments for patients with high-risk myelodysplastic syndromes.

### PICO system

Using the PICO system, the P corresponds to patients with high-risk myelodysplastic syndrome, I is the indicator of treatments of interest and the O the outcome (prognosis).

Thus, 24 studies were found and selected to answer this clinical question (Appendix I).

## What treatments exist for high-risk myelodysplastic syndromes?

### Introduction

For high-risk patients, treatment objectives are to delay disease progression and prolong survival. Thus, treatment

strategies are influenced by age and comorbidities. Myelodysplastic syndromes (MDS) are the result of a multi-step process including changes in epigenetic mechanisms, such as in DNA methylation. Within this rational, hypomethylating drugs are potential pharmacological agents. Two drugs, decitabine and 5-azacytidine (5-aza), have been extensively studied in the treatment of high-risk MDS.<sup>1</sup> (A) 5-Aza and decitabine were authorized for use in MDS by the USA Food and Drug Administration (FDA) in 2004 and 2006, respectively.

### 5-Azacytidine

5-Aza is a nucleoside analog with antitumor action. Its reduced metabolites inhibit DNA methyltransferase, the enzyme responsible for methylation during DNA synthesis, resulting in the synthesis of hypomethylated DNA with consequent changes in transcription and gene expression.

\* Corresponding author.

E-mail address: [silviamm@ufc.br](mailto:silviamm@ufc.br) (S.M. Magalhães).

<https://doi.org/10.1016/j.htct.2018.05.013>

2531-1379/© 2018 Published by Elsevier Editora Ltda. on behalf of Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. This is an open access article under CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

One hundred and ninety-one patients with MDS received either 5-aza (75 mg/m<sup>2</sup>/day subcutaneously for 7 days every 28 days) or clinical support. Responses were achieved in 60% of patients who received 5-aza (7% complete response, 16% partial and 37% improvement in hematological parameters) compared to 5% (improvement) in those who received clinical support ( $p$ -value < 0.001). The median time to leukemic transformation or death was 21 months for the 5-aza group vs. 13 months for clinical support ( $p$ -value = 0.007). Survival analysis using 6 months as the cutoff point (comparing patients randomized to receive 5-aza with those who started 5-aza treatment after less than 6 months of clinical support and those who remained in the clinical support group or started 5-aza treatment after 6 months) found that the median survival was 18, 14 and 11 months, respectively. Patients treated with 5-aza had a better overall survival (OS) compared to the group who received support alone ( $p$ -value = 0.003). Transformation to acute myeloid leukemia (AML) occurred as the first event in 15% of the patients in the 5-aza group and in 38% of those who received support ( $p$ -value = 0.001)<sup>1</sup> (A).

In another study, 358 patients with high-risk MDS were randomly assigned to receive conventional treatment (clinical support, low doses of cytarabine or chemotherapy) or 5-aza (75 mg/m<sup>2</sup> for 7 days subcutaneously every 28 days for at least six cycles). After a median follow-up of 21.1 months, the median OS was 24.5 months in the 5-aza group compared to 15 months in the conventional treatment group ( $p$ -value = 0.0001); after 2 years of follow-up, the OS was 50.8 and 26.2%, respectively ( $p$ -value < 0.0001). OS was better with 5-aza for all cytogenetic subtypes, especially for patients with -7/7q-. The mean time of progression to AML was 17.8 months for the 5-aza group compared to 11.5 months for the conventional treatment group ( $p$ -value < 0.0001). The proportion of patients with complete and partial remission was significantly higher in the 5-aza group (29%) than in the conventional treatment group (12%). There was a better rate of transfusion independence (45% vs 11%;  $p$ -value < 0.0001) and reduction to 33% for the need for intravenous antibiotics in the 5-aza group compared to the best conventional treatment group<sup>2</sup> (A).

### Decitabine

Decitabine (5-aza-2'-deoxycytidine) indirectly depletes methylcytosine, leading to hypomethylation of target promoter genes. It was approved for patients with or without previous treatment for de novo MDS or secondary MDS, in all French-American-British (FAB) subtypes and for intermediate, high-risk and very high-risk disease according to the revised international prognostic scoring system (IPSS-R).

In an open, randomized 1:1 multicenter study in the USA and Canada, 170 MDS patients were randomized for decitabine (15 mg/m<sup>2</sup> IV) for 3 h every 8 h for 3 days (135 mg/m<sup>2</sup> dose per cycle) repeated every 6 weeks or the best supportive treatment. According to the International Working Group (IWG) 2006 criteria, there was a better response rate (17%) including complete response (9%) in the decitabine group ( $p$ -value < 0.001). The median response time of 10.3 months was associated with transfusion independence. Intermediate-2 and high-risk patients (IPSS) presented greater OS than the group that received supportive treatment (12 months vs. 6.8 months;

$p$ -value = 0.03). There was also a higher rate of cytogenetic remission (35% vs. 10%) and hematological improvement (30% vs. 7%)<sup>3</sup> (A).

In a randomized trial, decitabine was compared to the best supportive care by the European Organization for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. This trial included 233 patients with intermediate-2 or high-risk MDS according to the IPSS, who were aged 60 years or older and ineligible for chemotherapy. Decitabine was infused at the dose of 15 mg/m<sup>2</sup> for 4 h, 3 times a day, for 5 days with this cycle being repeated every 6 weeks. OS was 10.1 months for the decitabine group and 8.5 months for the support group ( $p$ -value = 0.38), with a lower rate of leukemic transformation in the first group (22% vs. 33%;  $p$ -value = 0.036). There were better response (13% vs. 0%), partial response (6% vs. 0%) and hematologic improvement rates (15% vs. 2%) and higher rates of grade 3 and 4 febrile neutropenia (22% vs. 7%) in the group treated with decitabine<sup>4</sup> (A).

Thirty-seven patients with intermediate- or high-risk MDS (IPSS) received 15–20 mg/m<sup>2</sup> of intravenous decitabine given for 1 h daily for 5 days every 4 weeks. Patients receiving the 20 mg dose ( $n$  = 34) had more grade 3 or higher non-hematological toxicity, including cerebral infarction ( $n$  = 1) and subdural hematoma ( $n$  = 1). Myelosuppression was frequent, and 17 patients received granulocyte colony-stimulating factor (G-CSF). One patient had grade 4 neutropenia and was excluded from the study. Of the 37 patients, complete response, partial response, complete bone marrow response and hematological improvement as defined by the IWG 2006 criteria<sup>5</sup> (D) were observed in seven (18.9%), three (8.1%), two (5.4%) and four (10.8%) patients, respectively. At baseline, the percentage of transfusion-independent patients was 26%; after five treatment cycles, this percentage increased to 41% of patients. The 2-year leukemia-free survival rate was 52%<sup>6</sup> (B).

A randomized study compared 77 patients with advanced stages of MDS and 18 patients with chronic myelomonocytic leukemia taking three different treatment regimens with decitabine: 20 mg/m<sup>2</sup> intravenously daily for 5 days, 20 mg/m<sup>2</sup> subcutaneously daily for 5 days and 10 mg/m<sup>2</sup> intravenously daily for 10 days. The first scheme was chosen as optimal, leading to the highest complete response rate (39% vs. 21% vs. 24%, respectively;  $p$ -value < 0.05)<sup>7</sup> (A).

A meta-analysis of 11 studies and 1392 patients was performed to compare the efficacy, toxicity and survival after azacitidine and decitabine treatment. Partial response and hematologic improvement were significantly better with azacitidine. When compared to supportive therapy, only azacitidine was able to show improvements in OS and time of progression to leukemia. There was no difference between the two drugs with respect to complete response, transfusion independence or grade 3 and 4 hematological toxicity. Especially for over 75-year-old, high-risk patients, azacitidine is recommended as the first line treatment as it induces a better overall response and longer survival<sup>8</sup> (B).

In a study of prognostic predictors of the response to azacitidine involving 282 high-risk patients, performance status, unfavorable cytogenetics, presence of peripheral blood blasts and transfusion dependence were identified as independent adverse risk factors<sup>9</sup> (B).

Only retrospective studies with small numbers of cases aimed to evaluate the possible benefit of sequential treatment using hypomethylating drugs to treat high-risk MDS.

### ***Decitabine plus thalidomide***

The efficacy of the combination of thalidomide and decitabine was evaluated in a randomized study. Thalidomide is a low-cost drug with broad immunomodulatory effects, such as downregulation of tumor necrosis factor alpha, upregulation of adhesion molecules and inhibition of angiogenesis.

Seventy-five high-risk IPSS patients received thalidomide plus decitabine or decitabine alone. Overall, 2-year survival for the first group was higher than for the second (50.6% vs. 40.2%;  $p$ -value < 0.05). Overall response, complete and partial response, AML-free survival and side effects did not present any statistically significant differences between the two groups<sup>10</sup> (B).

## **Recommendations for use of hypomethylating agents**

Compared to conventional therapies, treatment with 5-azacitadine prolongs OS and decreases the risk of progression to AML in patients with high-risk MDS. Decitabine increases the response rate and transfusion independence and reduces the risk of leukemic transformation when compared to supportive treatment. Studies are inconsistent about the improvement in OS.

Thalidomide associated with decitabine increases OS compared to decitabine alone. Overall, complete and partial response rates, AML-free survival and side effects are not significantly different between thalidomide associated with decitabine and decitabine alone.

### ***Low-dose chemotherapy***

Low doses of cytarabine (Ara-C) and oral melphalan have been used in patients with MDS.

In a randomized, phase III study, 141 MDS patients were randomized to receive low doses of Ara-C (10 mg/m<sup>2</sup> twice daily subcutaneously) or supportive therapy. There was no difference in OS or time of progression to AML. There was a higher rate of infection and greater transfusion independence in the group treated with Ara-C<sup>11</sup> (A).

Two non-randomized studies with a small number of patients with MDS or AML treated with low doses of melphalan (2 mg/day orally) showed a complete response rate of around 30%; in one study, the median response was 14.5 months<sup>12,13</sup> (B).

### ***Intensive chemotherapy***

One study randomized high-risk MDS patients to receive conventional therapy (clinical support, low doses of cytarabine or chemotherapy) or 5-aza (75 mg/m<sup>2</sup> for 7 days every 28 days for at least six cycles). The results failed to demonstrate differences in the survival of patients treated with chemotherapy

or 5-aza, probably because of the small number of patients who participated<sup>2</sup> (A).

A retrospective study compared intensive chemotherapy or decitabine therapy in MDS matched according to risk calculated by the IPSS. Patients showed a higher OS and a lower mortality rate after induction with decitabine<sup>14</sup> (B).

Other studies using polychemotherapy regimens similar to those used for AML were tested but not in the form of randomized trials. Multiple chemotherapy regimens (topotecan-cytarabine, idarubicin-cytarabine and cyclophosphamide and fludarabine-cytarabine) used in a study of 510 patients with high-risk MDS had a complete response rate of 55%, induction mortality of 17% and survival rate of 8% in 5 years. Younger patients with normal karyotypes had a better overall response and the topotecan scheme had the lowest rate of complications<sup>15</sup> (B).

The FLAG regimen (fludarabine, high-dose cytarabine and G-CSF) was used in 42 patients with MDS (refractory anemia with excess blasts and refractory anemia with excess blasts in transformation) resulting in a complete remission rate of 74%, induction-related death of 9% and resistance of 17% with a median remission duration of 13 months. The presence of complex karyotypes conferred a worse response<sup>16</sup> (B).

### ***Hematopoietic stem-cell transplantation***

Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only curative modality for MDS. The results are quite diverse in relation to disease-free survival (30–50%), treatment-related mortality (37–68%) and relapse (24–58%) in respect to the different modalities (related, unrelated, myeloablative or reduced intensity) and the different sources of cells (bone marrow, peripheral blood) performed at various stages of the disease, with or without previous treatments and in different centers. Therefore, less than half of the patients are cured. The treatment fails in most cases due to treatment-related mortality (TRM) and, currently, mainly due to relapse of the disease. Factors that affect treatment failure are related to the disease (percentage of blasts, cytopenias, bone marrow fibrosis, cytogenetics and mutations that are mainly related to relapse), to the patient (age, performance status, comorbidities, and transfusion dependence with a significant impact on TRM) and to factors related to transplantation that affect both relapse and TRM. A prognostic score system for the evolution of patients submitted to allogeneic transplantation in MDS was recently proposed based on the analysis of 2173 patients<sup>17</sup> (B).

A randomized phase III study compared the results of allogeneic vs. autologous HSCT and chemotherapy in patients with MDS (intermediate—1, intermediate—2, high-risk IPSS) or AML secondary to MDS. This study analyzed 168 patients who achieved complete remission after one cycle of chemotherapy. Those who had compatible human leukocyte antigen (HLA) siblings were referred for allogeneic HSCT after one cycle of consolidation chemotherapy. Patients without donors who had achieved complete remission after the consolidation regimen were randomly assigned to a second course of consolidation or autologous HSCT with peripheral blood hematopoietic stem cells. Having an HLA-compatible donor resulted in better disease-free survival in patients with

intermediate or poor cytogenetic characteristics, whereas no significant difference was observed between patients with or without donors in a low-risk cytogenetic category. Autologous transplantation did not improve survival compared to intensive chemotherapy<sup>18</sup> (A).

The intensity of the myeloablative or reduced-intensity conditioning regimen was studied in two prospective randomized clinical trials. One was interrupted early due to the high incidence of relapse in the reduced-intensity conditioning group<sup>19</sup> (B).

In the second study, conducted by the European Society of Bone Marrow Transplantation (EBMT) in 129 patients, no significant differences were observed for TRM or relapse between the arms<sup>20</sup> (B). HLA-identical related transplantations are still the best option.

More recently, on analyzing 1728 patients using the IPSS-R and the “continuous-time multi-state model”, one study reported a better life expectancy for patients whose HSCT was delayed from low-risk categories to intermediate-risk in younger patients and in those who had hypomethylated DNA before transplantation<sup>21</sup> (B).

A consensus of recommendations for allogeneic transplantation in MDS was published by the EBMT and LeukemiaNet<sup>22</sup> (D).

## Recommendations

In the absence of randomized studies, the use of chemotherapeutic agents of AML-like regimens is suggested for under 65-year-old MDS patients with more than 10% of blasts and good prognosis cytogenetics, who are candidates for treatment intensification with allogeneic HSCT. Disease risk score and presence of comorbidities are recognized as relevant clinical variables for HSCT eligibility. Fit patients with higher-risk IPSS-R and those with lower-risk IPSS-R with poor-risk genetic features, profound cytopenias and high transfusion burden are candidates for HSCT. Patients with a very high MDS transplantation risk score have little chance of cure with standard HSCT. For patients with contraindications for high-intensity conditioning regimens, reduced intensity conditioning should be considered.

## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Appendix I

### 1. Clinical question

What treatments exist for high-risk MDS?

### 2. Structured question (PICO)

Patients with high-risk MDS

Intervention hypomethylating agents (5-azacytidine and decitabine)

Low-dose chemotherapy (low-dose ARA-C, melphalan)

Polychemotherapy as in the treatment of AML

Hematopoietic stem-cell transplantation

Support therapy

Outcome prognosis/treatment

### 3. Initial eligibility criteria for studies

- Components of PICO
- No time limit
- No limit of languages
- Full text availability

### 4. Search strategies

#1: (Myelodysplastic syndrome OR myelodysplastic syndromes OR dysmyelopoietic syndromes OR dysmyelopoietic syndrome OR hematopoietic myelodysplasia OR hematopoietic myelodysplasias) = 23 074 studies

### 5. Selection of articles

Initially selected by the title, sequentially by the abstract and finally by the full text, the latter being subjected to critical evaluation and extraction of outcomes related to the outcomes.

### 6. Critical evaluation and strength of evidence

The strength of the evidence of the studies was defined taking into account the study design and the corresponding risks of bias, the results of the analysis (magnitude and precision) and relevance and applicability (Oxford/GRADE).<sup>23,24</sup>

## REFERENCES

1. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of 5-azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol.* 2002;20(10):2429–40.
2. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of 5-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.
3. Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106(8):1794–803.
4. Lübbert M, Suciu S, Baila L, Rüter BH, Platzbecker U, Giagounidis A, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *Clin Oncol.* 2011;29(15):1987–96.
5. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood.* 2006;108(2):419–25.
6. Oki Y, Kondo Y, Yamamoto K, Ogura M, Kasai M, Kobayashi Y, et al. Phase I/II study of decitabine in patients with myelodysplastic syndrome: a multi-center study in Japan. *Cancer Sci.* 2012;103(10):1839–47.
7. Kantarjian H, Oki Y, Garcia-Manero G, Huang X, O'Brien S, Cortes J, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood.* 2007;109(1):52–7.
8. Xie M, Jiang Q, Xie Y. Comparison between decitabine and azacitidine for the treatment of myelodysplastic syndrome: a

- meta-analysis with 1392 participants. *Clin Lymphoma Myeloma Leuk.* 2015;15(1):22–8.
9. Itzykson R, Thépot S, Quesnel B, Dreyfus F, Beyne-Rauzy O, Turlure P, et al., Groupe Francophone des Myelodysplasies (GFM). Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacytidine. *Blood.* 2011;117(2):403–11.
  10. Zhao WH, Zeng QC, Huang BT, Li BS, Chen RL. Decitabine plus thalidomide yields more sustained survival rates than decitabine monotherapy for risk-tailored elderly patients with myelodysplastic syndrome. *Leuk Res.* 2015;39(4):424–8.
  11. Miller KB, Kim K, Morrison FS, Winter JN, Bennett JM, Neiman RS, et al. The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndromes: a phase-III intergroup study. *Ann Hematol.* 1992;65(4):162–216.
  12. Omoto E, Deguchi S, Takaba S, Kojima K, Yano T, Katayama Y, et al. Low-dose melphalan for treatment of high-risk myelodysplastic syndromes. *Leukemia.* 1996;10(4):609–14.
  13. Denzlinger C, Bowen D, Benz D, Gelly K, Brugger W, Kanz L. Low-dose melphalan induces favourable responses in elderly patients with high-risk myelodysplastic syndromes or secondary acute myeloid leukaemia. *Br J Haematol.* 2000;108(1):93–5.
  14. Kantarjian HM, O'Brien S, Huang X, Garcia-Manero G, Ravandi F, Cortes J, et al. Survival advantage with decitabine versus intensive chemotherapy in patients with higher risk myelodysplastic syndrome: comparison with historical experience. *Cancer.* 2007;109(6):1133–7.
  15. Kantarjian H, Beran M, Cortes J, O'Brien S, Giles F, Pierce S, et al. Long-term follow-up results of the combination of topotecan and cytarabine and other intensive chemotherapy regimens in myelodysplastic syndrome. *Cancer.* 2006;106(5):1099–109.
  16. Ferrara F, Leoni F, Pinto A, Mirto S, Morra E, Zagonel V, et al. Fludarabine, cytarabine, and granulocyte-colony stimulating factor for the treatment of high risk myelodysplastic syndromes. *Cancer.* 1999;86(10):2006–13.
  17. Shaffer BC, Ahn KW, Hu ZH, Nishihori T, Malone AK, Valcárcel D, et al. Scoring system prognostic of outcome in patients undergoing allogeneic hematopoietic cell transplantation for myelodysplastic syndrome. *J Clin Oncol.* 2016;34(16):1864–71.
  18. de Witte T, Hagemeijer A, Suciu S, Belhabri A, Delforge M, Kobbe G, et al. Value of allogeneic versus autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia: final results of a prospective randomized European Intergroup Trial. *Haematologica.* 2010;95(10):1754–61.
  19. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol.* 2017;35(11):1154–61.
  20. Kröger N, Iacobelli S, Franke GN, Platzbecker U, Uddin R, Hübner K, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a randomized phase III study of the EBMT (RICMAC Trial). *J Clin Oncol.* 2017;35(19):2157–64.
  21. Della Porta MG, Jackson CH, Alessandrino EP, Rossi M, Bacigalupo A, van Lint MT, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelo-dysplastic syndrome stratified according to the revised International Prognostic Scoring System. *Leukemia.* 2017;31(11):2449–57.
  22. De Witte T, Bowen D, Robin M, Malcovati L, Niederwieser D, Yakoub-Agha I, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood.* 2017;129(13):1753–62.
  23. Goldet G, Howick J. Understanding GRADE: an introduction. *J Evid Based Med.* 2013;6(1):50–4.
  24. Levels of Evidence and Grades of Recommendations, Oxford Centre for Evidence Based Medicine. Available from: [http://cebm.jr2.ox.ac.uk/docs/old\\_levels.htm](http://cebm.jr2.ox.ac.uk/docs/old_levels.htm)