SINDROMES MIELODISPLÁSTICAS
AGENTES HIPOMETILANTES somente para risco mais alto?

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RISK STRATIFICATION

- refractoriness to 1st line
- transfusion dependency

Dynamic assessment of RBC-transfusion dependency improves the prognostic value of the revised-IPSS in MDS patients at any time during the course of MDS is associated with poor OS, independent of IPSS-R.

MDS - TREATMENT

HIGH RISK
NCCN Guidelines Version 2.2019
Myelodysplastic Syndromes

PROGNOSTIC CATEGORY
IPSS-R: Intermediate, High, Very High
IPSS: Intermediate-2, High
WPSS: High, Very High

TREATMENT

Allo-HCT or Azacitidine followed by allo-HCT or Decitabine followed by allo-HCT or High-intensity chemotherapy followed by allo-HCT

Yes

Transplant candidate

Azacitidine (preferred) (category 1) or Decitabine or Clinical trial

No

Relapse after allo-HCT or No response

Consider allo-HCT or donor lymphocyte infusion or Azacitidine or Decitabine or Clinical trial

Response → Continue

No response or relapse → Clinical trial or Supportive care
HYPOMETHYLMANTING AGENTS

- Response after 4 to 6 cycles
- CR in 20% to 30%
- Hematologic improvement/stable disease: 50%
- Improved survival: 9.5 months
- Resistance or loss of response: OS < 6 months
- Most patients relapse in 2 years

AZACITIDINE 75 mg/m2/day, SC, 7 days, every 28 days
DECITABINE 20 mg/m2/day, IV, 5 days, every 28 days
A systematic review and network meta-analysis comparing azacitidine and decitabine for the treatment of myelodysplastic syndrome

Almasri J et al Systematic Reviews 2018; 7:144.
Conclusions

Azacitidine and decitabine are both likely to be superior to BSC. The available indirect evidence comparing the two agents warrants very low certainty and cannot reliably confirm the superiority of either agent. Head-to-head trials are needed to provide a better understanding of the relative effectiveness of azacitidine and decitabine. In the meantime, the choice of agent should be driven by patients’ preferences, drug availability and adverse effects, and cost.

Azacitidine significantly improved OS when compared to BSC

Fenaux, 2009

Almasri J et al Systematic Reviews 2018); 7:144.
Response rates are similar for both drugs. Survival benefit from a phase III randomized trial is reported for azacitidine and not for decitabine. Both drugs should be continued for at least 4–6 cycles to assess response. In patients who have clinical benefit, continue treatment.
Although a number of publications on predictive markers for response to AZA exist, results are inconsistent and improved response rates did not translate to improved OS.

Mutations in the DNA methylation pathway predict clinical efficacy to hypomethylating agents in myelodysplastic syndromes: a meta-analysis

A total of 13 cohort studies, covering 1398 patients with MDS treated by HMAs were included

• DNMT3A mutations had a favorable impact on ORR (p=0.008)
• TET2 mutations had a no significant favorable impact on ORR (p=0.06)

None advantages of mutations on ORR translated into a benefit in overall survival

Du M et al, Leuk Res, 2019 Mar [Epub ahead of print]
lower- or intermediate-risk patients, who failed in first-line therapy, should be handled as higher-risk
Incorporation of molecular data into the Revised International Prognostic Scoring System in treated patients with myelodysplastic syndromes

- age
- IPSS-R
- EZH2
- SF3B1
- TP53

C-index (0.73)
IPSS-R (0.67)

Values over 0.7 indicate a good model.

MDS - TREATMENT
THE QUESTION OF THE OPTIMAL ORDER OF LENALIDOMIDE AND HMA USE AFTER ESA FAILURE
In a retrospective analysis, rates of erythroid improvement were significantly higher when *lenalidomide* was used as first-line rather than second-line treatment (38% vs. 12%) \((p = .04)\)


Longer treatment duration and survival with LEN-HMA support first-line use of *lenalidomide* in MDS in sequence with HMAs.

Zeidan AM et *Leuk Lymphoma* 2019 Jan [Epub ahead of print].
Outcome of lower-risk patients with myelodysplastic syndromes without 5q deletion after failure of erythropoiesis-stimulating agents.

International retrospective cohort of 1,698 patients with non-del(5q) lower-risk MDS treated with ESAs (response 61.5%) with primary failure or relapse after a response

None of the most commonly used second-line treatments (HMA and LEN) significantly improved OS

Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion

a randomized phase III study

In an intent-to-treat (ITT) analysis, erythroid response (IWG 2006 criteria) after four treatment cycles was 23.1% (95% CI 13.5–35.2) in the L arm and 39.4% (95% CI 27.6–52.2) in the LE arm (P = 0.044)

RBC-T I response and median response duration: not significant

Toma A et al Leukemia 2016; 30: 897.
No response after 3 mo or erythroid response followed by loss of response

Lenalidomide\textsuperscript{cc} + EPO

\textsuperscript{cc} Lenalidomide 10 mg/d for 21 out of 28 days if ANC >0.5 and platelets >50,000 Thoma A et al \textit{Leukemia} 2016; 30: 897
HYPOMETHYLATING AGENTS

• STANDARD DOSE
• REDUCED DOSE
• ORAL FORMULATION

LOW RISK
Randomized phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN

**azacitidine** 75 mg/m² IV/SC daily or **decitabine** 20 mg/m² IV daily for **3 consecutive days** on a 28-day cycle.

• The ORRs were **70%** and **49%** (p = .03) for patients treated with **decitabine** and azacitidine, respectively (median number of cycles: 9)

• The use of low-dose HMAs is **safe and effective** in patients with lower-risk MDS. Their effect on the natural history of lower-risk disease **needs to be further studied**.

Jabbour E et al  *Blood* 2017; 130: 1514.
Some studies have demonstrated clinical benefit with low doses of azacitidine or decitabine for lower-risk MDS. Jabbour E et al. Blood 2017; 130 : 1514.
PHASE II DECITABINE (DAC) VERSUS AZACITIDINE (AZA) IN MYELODYSPLASTIC SYNDROME (MDS)

decitabine 3 days or azacitidine 3 days versus azacitidine 5 days

ClinicalTrials.gov Identifier: NCT02269280

Recruitment Status: Recruiting
First Posted: October 21, 2014
Last Update Posted: April 20, 2018

See Contacts and Locations

Sponsor: M.D. Anderson Cancer Center
Prospective randomized trial of 5 days azacitidine versus supportive care in patients with lower-risk myelodysplastic syndromes without 5q deletion and transfusion-dependent anemia

- The primary endpoint: erythroid improvement (HI-E) after 9 cycles
- HI-E: 44.4% Aza and 5.5% BSC (p<.01)
- No significant differences were observed in secondary endpoints (neutrophils HI, platelets HI, progression to AML, overall survival)
- VAF of some mutated genes (RET, SF3B1, ASXL1) decreased in Aza-responder patients

LR-MDS patients lacking del(5q) and resistant to ESAs, who receive 5 days Aza, achieve TI in a substantial proportion of cases and results in modifications in mutational landscape.
oral administration enables extended dosing regimens that **may prolong therapeutic effects** of azacitidine by increasing exposure to cycling malignant cells (300mg QD for 14 or 21 days per 28-day cycle)

**significant DNA hypomethylation through cycle end**

THE EFFICACY AND SAFETY OF ORAL AZACITIDINE PLUS BEST SUPPORTIVE CARE VERSUS PLACEBO AND BEST SUPPORTIVE CARE IN SUBJECTS WITH RBC TRANSFUSION-DEPENDENT ANEMIA AND THROMBOCYTOPENIA DUE TO LOW RISK MDS

ClinicalTrials.gov Identifier: NCT01566695

Recruitment Status: Active, not recruiting
First Posted: March 29, 2012
Last Update Posted: January 11, 2019

Sponsor: Celgene
• Apenas um subgrupo de pacientes responde a um dos tratamentos atualmente disponíveis e a maioria eventualmente perde a resposta

• A refratariedade ou perda de resposta à terapia de primeira linha está associada a mau prognóstico e menor sobrevida

• Drogas hipometilantes são consideradas primeira linha para o tratamento da SMD de **alto risco**, elegíveis ou não para o TMO
• Na SMD de **baixo risco**, hipometilantes são atualmente indicados para anemia dependente de transfusão, após refratariedade à primeira linha, preferencialmente após associação lenalidomida/EPO (off label). Não foi demonstrada vantagem de sobrevida.

• Segurança e eficácia do uso de hipometilantes em baixas doses ou formulação oral aguardam resultados de estudos em andamento.
SINDROMES MIELODISPLÁSTICAS
AGENTES HIPOMETILANTES
samente para risco mais alto?

NÃO

"the jury is still out"
Guidelines on myelodysplastic syndromes: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular

Silvia Maria Meira Magalhães, Lígia Niero-Melo, Maria de Lourdes Lopes Ferrari Chauffaille, Elvira Deolinda Rodrigues Pereira Velloso, Irene Lorand-Metze, Renata Buzzini, Wanderley Marques Bernardo.

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MYELODYSPLASTIC SYNDROMES

Treatment of MDS

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