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# Low-risk MDS: non-transplant therapeutic approach

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## Summary

A significant progress has been made over the last couple of decades in understanding the biology and treatment of myelodysplastic syndromes. Based on several parameters (% blasts, cytogenteics, number of affected lineages) the patients are classified as having a lower-risk (LR) or higher risk disease. Here, we will focus on LR-MDS.

The patients with LR-MDS are treated with RBC transfusions as needed, with or without erythroid stimulating agents. Luspatercept, an activin analogue, is a reasonable second line agent. Among the investigational agents in this field we can mention ruxodustat (a HIF inhibitor) and imetelstat, a telomerase inhibitor. Treatment of thrombocytopenia remain challenging and an open question.

## Keywords

Myelodysplastic syndrome, low-risk, diagnostics, management, targeted therapy.

## Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell (HSC) disorder characterised by ineffective hematopoiesis accompanied by blood cytopenia and by common progression to acute myeloid leukemia (AML). MDS is mostly observed in the elderly persons [1-4]. The main clinical features of MDS are as follows:

- **Clonal** hematopoietic stem-cell disease(s);
- **Abnormal** differentiation, maturation, impaired apoptosis;
- Genetic (Immune) basis;
- Median age: 74 years;
- Incidence increases with age;
- 40-50 per 100 000 in > 70 yr;
- **Anemia** (90%); Pancytopenia (50%);
- **AML Transformation** (20%-60%).

The cytomorphological examination in MDS is based on detection of bi- or tri-lineage dysplasia in different hematopoietic lineages in the bone marrow and/or peripheral blood, and enumeration of blast cells in the samples (Fig. 1A, B).

## Classification

MDS patients are classified by International Prognostic Scoring System (IPSS):

- **Prognostic** Parameters:
  - FAB subtype: BM morphology – **% blasts**;
  - **Cytogenetics;**
  - "good" *vs* "bad" types;
  - **# Lineages affected**.
- **IPSS:**
  - Low-risk; Intermediate-1 – **Lower risk** disease;
  - Intermediate-2; High – **Higher risk** disease.
- **IPSS-R:**

Very low; Low; Intermediate; High; Very high [5, 6].

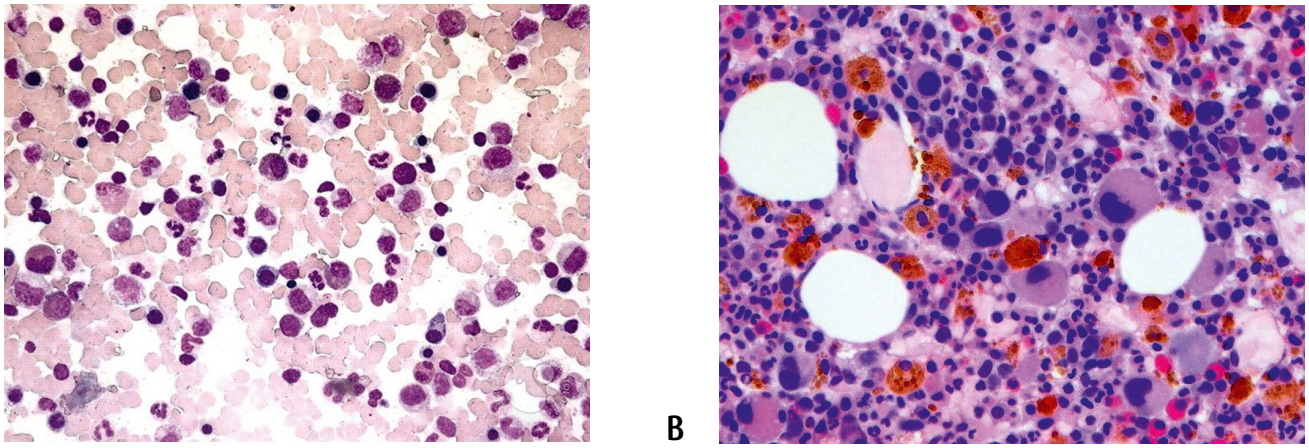

**Figure 1. General pattern of bone marrow in healthy person (A) and MDS patient (B). BM of MDS patients is characterized by altered (hyper or hypo-) cellularity, numerical (hyper or hypo-) changes, morphological abnormalities in one or more hematological lineages, and potential increased % of blasts.**

**Evaluation of Treatment Response – Not Blac & White:- Thus, standard response criteria were proposed:**

- **International Working Group (IWG) 2000/2006 [5, 6]:**
  - Complete response (**CR**);
  - Marrow CR (mCR); (Partial R);
  - Cytogenetic response (Cyt R);
  - Hematologic improvement (**HI**);
    - Erythroid (**HI-E**); Neutrophil (HI-N); Platelet (HI-P).
- **IWG 2018: HI-E – Erythroid response [7]:**
  - **Transfusion burden:**
    - Non (0/16 wk), **Low** (3-7); **High** > 8;
    - Response: minor (50% less) or major (TI).

## MDS treatment

General Strategy of MDS Treatment depends on the disease status (IPSS/R), by discerning lower-risk cases (IPSS: Low risk; Intermediate-I), and higher-risk MDS (IPSS: Intermediate-II; High risk cases).

Patient factors should be taken into account:

- Age; co-morbidities; functional status;
- Quality of life (QoL); Pt reported outcomes (PRO).

MDS treatment is often consistent with a general 'Rule of Thumb':

- Response of about 50%;
- Response duration about 2 yr.

This is true for the following therapeutic approaches:

- RBC Transfusions;
- Erythroid stimulating agents (ESAs) ;
- Lenalidomide;
- Hypomethylating agents (HMA);
- Stem Cell Transplant (SCT).

The remaining challenges include: increasing response rate and duration of response and, finally, achieving cure of this disorder.

My experience with MDS could be traced from the Hematology-Oncology Fellowship – GW-NIH (USA) 1986-1989 at George Washington University Medical Center – Department of Hematology-Oncology (Fig. 2).


**Figure 2. Hematology research team at the George-Washington University (I am sitting, second on the right).**

Recently, the European MDS Registry (EUMDS) is a prospective multicentre European registry for myelodysplastic syndromes (MDS), being the first international prospective, observational registry for newly diagnosed IPSS low- and intermediate-1 risk MDS patients. 18 countries participate in EUMDS activities, i.e., Austria, Chech Republic, France, Germany, Greece, Italy, Netherlands, Romania, Spain, Sweden, UK, Denmark, Portugal, Poland, Israel, Serbia, Croatia, Switzerland.

Appropriate Guidelines were issued by EUMDS (2019) (see MDS-Europe in the net).

## Managing lower risk MDS

80% of MDS patients have a hemoglobin <10 g/dl at diagnosis, the majority become transfusion-dependent.

Therefore, MDS treatment for anemia still includes multiple RBC transfusions. Most of these patients received MDS-specific supportive care, including RBC transfusions in 50% of the cases [8].

## RBC Transfusions in MDS (I)

RBC transfusions are the mostly used (50%) in low-risk MDS. For those patients who were transfusion-independent at diagnosis, the mean interval between diagnosis and the first transfusion was 249 days [9]. For symptomatic anemia, however, limited evidence was shown.

Complications of RBC transfusions in MDS patients include the following events:

• Volume-related; TRALI (Transfusion-Related Acute Lung Injury); ABO incompatibility;

• RBC allo-immunization in 30% of cases [10]. Having MDS is suggested to be an independent risk factor contributing to production of RBC alloantibodies.

Iron overload due to multiple RBC transfusions is among complication of supportive therapy in MDS [11-12]. E.g., the transfusion dose density is associated with shorter progression-free survival (PFS) and worse quality of life. It showed an inverse correlation with PFS ($P<1\times10^{-4}$): the dose density had an increasing effect until 3 units/16 weeks [13].

## RBC Transfusions in MDS (II): ELN-EUMDS 2019 Guidelines

The questions arising:

• Hb threshold for starting the transfusions?
  – < 7 g/dl (most centers will transfuse if and when Hb < 7g/dl);
  – Individualize (Grade B, level 1).

• Hb target levels?
  – No target (Grade C, level 2) – recommendation – activate local policy.

• Transfusion frequency?
  – Individualize (C-2).

• Prophylactic RBC Ag matching ? No (C-2)

• Symptomatic benefit *vs* toxicity ?
  – Individualize (C-2).

For reference see [14]: Bowen D, Mittelman M, ELN-EUMDS Guidelines (2019; online).

Effects of erythrocyte-stimulating agents (ESA) in low-risk MDS anemia were summarized for 2020. ESA were applied as first-line therapy (without RBC transfusions) and proved to be effective in a series of studies, as shown by Hb rise, fewer RBC transfused, improved QoL, with documented safety for the patients [15-19]. Hematological response was observed in a sufficient group of MDS patients (Table 1).

Therapeutic efficiency and safety of different erythrocyte-stimulating agents (ESAs) in LR-MDS was proven over 3 decades. E,g, darbopoietin A was tested in phase 3 trial (n=147), with ORR of 59% [21]. A randomized study of Epoetin-α (phase 3 trial) enrolled 130 cases, with 46% overall response rate [22]. A meta-analysis of different ESA in LR-MDS has shown an ORR of 45-73%, and, possibly, longer overall survival of MDS patients, with 50% response [23]. Finally, a large study by EUMDS included a cohort of LR-MDS patients, at median duration of ESA therapy for 27.5 months, delayed RBC transfusions (by 6 to 23 months), lower risk of death; similar risk of progression to AML, along with safety of such treatment [24].

A team from Denmark found only marginal effects (RR 1.1-1.9) of ESA upon risk of venous thromboembolism (VTE) and strokes in a cohort of 2114 patients [25]. In general, the response rate to ESA in MDS was 50% at the 2-year terms, and proven safety.

**Table 1. Initial results on recombinant human Epo (rHuEPO) in MDS. The responding patients are shown in bold [20].**

| Patient | Age / Gender | FAB | sEPO mU/mL | Hb (g/dL) Week 0 | Hb (g/dL) Week 8 |
|---|---|---|---|---|---|
| 1. ZS | 82 M | RARS | 300 | 8.0 | 8.2 |
| 2. GA | 79 M | RARS | - | 7.8 | 8.0 |
| 3. DG | 79 F | RARS | 550 | 7.9 | 8.0 |
| 4. JL | 75 F | RARS | 480 | 8.1 | 7.7 |
| 5. BB | 74 F | RARS | 660 | 8.3 | 8.0 |
| 6. DA | 78 F | RARS | 600 | 8.1 | 8.0 |
| **7. SB** | **73 F** | **RA** | **75** | **8.0** | **11.0** |
| 8. GK | 68 F | RARS | - | 8.2 | 8.3 |
| 9. SY | 65 M | RARS | - | 7.8 | 8.1 |
| **10. SM** | **59 F** | **RA** | **471** | **8.9** | **9.4** |
| 11. AF | 80 M | RA | 500 | 7.3 | 6.9 |
| 12. MBB | 68 F | CMML | 400 | 8.0 | 7.8 |
| **13. IS** | **82 F** | **RA** | **96** | **7.4** | **11.9** |

## EPO non-erythroid (immunologic) effects

Therapeutic efficiency of rhEPO was documented in myeloma-associated anemia [26]. Moreover, probable anti-neoplastic effects of erythropoietin were shown in experimental murine myeloma [27, 28].

Other events associated with erythropoietin therapy in patients with hematological disorders include a decreased glucose level [29], probable bone loss by targeting monocytes and osteoclastic activity in murine model [30], as well as decrease in serum IL-6 upon the EPO therapy [31], as seen in Fig. 3. In myelodysplastic syndrome, improvement of T cell immune functions was an additional positive effect observed after erythropoietin treatment [32].

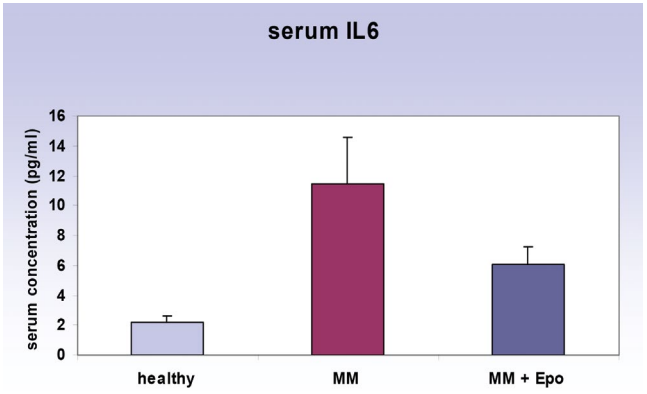


**Figure 3. Comparative IL-6 levels in blood serum of heathy persons, in MM patients, and in Epo-treated MM patients [31]**

ESA treatment may fail in sufficient part of MDS patients. Clinical outcomes in LR-MDS in the non-responsive cohort were studied by Park et al. [33].

The study represented a retrospective analysis of LR-MDS patients without 5q chromosome deletion. Of them, 653 experienced primary failure and 494 experienced relapse after a response. Median OS among ESA non-responders was 4.2 years in relapsing patients *versus* 3.7 years in primary failure. Second-line treatment was performed in 39% of them. Hypomethylating agents (HMA) were used in 336 patients, with 46% response, and lenalidomide, in 88 patients with 39% response rates. However, the five-year OS for patients receiving HMA, lenalidomide, or other therapies was 36.5%, 41.7%, and 51%, respectively ( P = .21). In a multivariable analysis, there was no significant OS difference among the three groups. Yes, we need to do better…

## Lenalidomide therapy

Several studies demonstrated efficiency of Lenalidomide in LR-MDS, either with or without 5q deletion. List et al. [34] have shown that transfusion demands were reduced in 76% of the treated patients with 5q chromosome deletion, and some of them did not longer require transfusions, regardless of the karyotype complexity. The response to lenalidomide occurred at the median time of 4.6 weeks and retained for a median of 2 years. In the meta-analysis by Lian et al. [35], overall rate of hematological erythrocyte response was 58%. The patients with 5q deletion had significantly higher rate of response, significantly prolonged overall survival and lower risk of AML progression. The drug showed a predictable and manageable safety profile in LR-MDS in terms of adverse effects [36]. P53 mutations with higher TP53 protein expression in BM progenitors of lenalidomide-treated patients proved to be associated with higher AML risk and shorter OS [37-39].

Below are main results of the MDS-004 study in Del (5q) MDS patients [38]:

- RRBC TI 56%; Cytogenetic response was observed in 50% at 10mg of Len daily
- Adverse effects: cytopenia, rash, gastrointestinal, thrombosis
- No effect on leukemic transformation

• Results with non-del (5q) patients: MDS-005 [39]

- Among a group of 239 pts (lenalidomide or placebo), transfusion independence was achieved in 27% (*vs* 2.5% with placebo) at 8 weeks of Len therapy.

## Other therapeutic targets

***TGF-binding drugs***

Hence, anemia remains a sufficient problem in some LR-MDS patients. What can we offer when ESA, or Lenalidomide treatment fail? Newer drugs, e.g., activin analogues, may potentially improve erythropoiesis, by TGF-b binding, or Smad2/3 inhibition. E.g., Luspatercept was tested in a PACE-MDS Trial (ACE-536) at the Phase II, (s/c injections, every 3 wk; 58 pts; post ESA), as reported by Platzbecker et al. [40]. The drug caused a significant dose-dependent increase in blood Hb contents, and, after 4-mo treatment at a dose of 0.75-1.75 mg/kg, reduced demands for RBC transfusions.

The MEDALIST study was a phase 3, randomized, double-blind, placebo-controlled trial with transfusion-dependent MDS. Luspatercept therapy led to RBC transfusion independence in lower-risk MDS patients resistant to ESA [41]. Of the 229 patients, 153 were randomly assigned to receive luspatercept or placebo, s/c every 3 weeks, for ≥ 24 weeks. Transfusion independence for 8 weeks or longer was observed in 38% of the patients in Luspatercept group *versus* 13% in the placebo group (P<0.001).

Sotatercept (ACE-011), a drug with similar action, was recently subject to phase 2 study carried out by Komrokji et al. [42]. 74 patients enrolled were ineligible for, or refractory to ESA therapy. Clinical response was documented in 40-50% (better outcomes in those with lower transfusion burden). Adverse effects manifested as diarrhea, bone pain, fatigue, GI, edema, lipase increase.

A special COMMANDS Trial aimed to compare Luspatercept *versus* erythropoietin is launched now [43].

***Low Dose/Oral hypomethylating agents (HMA) in LR-MDS***

A prospective trial (Phase 2) was performed using Azacitidine *versus* best supportive care (BSC). The primary endpoint was erythroid hematologic improvement which was achieved in 44.4% of cases after 9 treatment rounds, *versus* 5.5% of patients treated with BSC, as well as transfusion independence in all the drug responders for a median of 1 year [44].

Low-dose decitabine *versus* low-dose azacitidine (Aza) were applied in the phase II study [45]. A total of 113 patients were treated: 35% with Aza and 65% with Dec. The ORRs were 70% and 49% for Dec and Aza, respectively. Transfusion independence was achieved in 32 % of decitabine-treated patients, and the treatment was well tolerated.

A meta-analysis performed by Komrokji et al. (2018) [46] concerning efficiency of Aza in a total sample of 233 patients with, mostly, non-del(5q) LR-MDS has shown that the RBC transfusion independence was achieved in 39% of the cases, at ≥6 azacitidine treatment cycles.

Several years ago, a report on clinical effects of peroral Aza (cc-486) in LR-MDS was published [47]. The study included 216 MDS patients. The disease status was assessed after cycle 6. The ORR was 40%, including hematologic improvement in 28% of patients, and transfusion independence lasted for 56 days in 47% of initially transfusion-dependent cases.

Therefore, QUAZAR study (AZA-MDS-003) was continued as randomized controlled trial (RCT), Phase 3, in LR-MDS patients with anemia and thrombocytopenia [48]. The patients received CC-486 or placebo. 31% and 11% of patients, respectively, achieved RBC-TI in the main and placebo group, which lasted, for, respectively, 11.1 and 5.0 months. Platelet improvement rate was also higher in the CC-486 arm (24.3% *vs* 6.5%).

***Roxadustat (FG-4592)***

Usage of oral prolyl hydroxylase (PH) inhibitors may be a promising tool of anemia treatment, since the PH inhibition may stabilize hypoxia-inducible factor (HIF). This factor induces erythropoietin production and decreases hepcidin, thus promoting iron mobilization [49]. Recently, this drug was shown to be safe and efficient in the patients with anemia caused by chronic renal failure – CRF [50].

Roxadustat is another PH inhibitor(Fibrogen) undergoes a clinical FGCL-4592-082 trial which is an open label study including 24 pts, achieving 38% TI if used at a dose of 2.5 mg/kg, ×3/wk [51]. Now this drug is under phase 3, randomized controlled trial, with 156 patients.

***Telomerase inhibitors***

Clinical trials with Imetelstat, a telomerase inhibitor, were performed in the patients with LR-MDS anemia [52-54]. Phase 2 trial is an open, single arm study, with the drug dose of 7.5 mg/kg I/V q 4 wk. A subgroup of 38 LR-MDS patients were selected with transfusion dependence, ESA relapse/resistance, non-del(5q), being hypomethylating agent and lenalidomide naïve. Of them, 16 patients (42%) achieved transfusion independence. This effect was durable (a median of 21 mo) and accompanied by reduced telomerase activit. Phase 3 (a placebo-controlled study) is ongoing.

## Treatment of thrombocytopenia in MDS

Platelet transfusions (PLT) are made in MDS patients. However, there is no evidence on their efficiency. This procedure is indicated in cases of active bleeding and should be performed per local guidelines [14, 55]. In absence of active bleeding, the platelet transfusion cannot be routinely recommended!. One may consider "thrombostatics", e.g., Tranexamic acid, or Anti-fibrinolytic solutions, (Hexakapron).

***Romiplostim in MDS***

For the last decade, several groups study safety and efficacy of romiplostim, a synthetic protein, an analogue of thrombopoietin which increases platelet production, for treatment of MDS patients with thrombocytopenia. The phase I/II study by Kantarjan et al. [56] in 44 patients have shown a durable platelet response in 46% cases. After achieving platelet response (4 weeks) the patients were treated with romiplostim for up to 1 year. Serious adverse effects were registered in 11% of the cases, and 2 patients progressed to AML.

The Phase II study was arranged as a randomized, placebo-controlled trial which included a total of 250 LR-MDS patients randomized 2:1, to receive romiplostim or placebo weekly for 58 weeks [57]. The incidence of bleeding events was reduced in the romiplostim group, and platelet response rates proved to be higher in the patients who received romiplostim. However, study drug was stopped because of excess blasts and potential AML risk following this treatment. Later on, upon 5-year of this cohort, the percentages of patients with AML (12%) in romiplostim group were similar (11%) to those in placebo group, as shown by Kantarjian et al. [58]. In a special commentary, I emphasized that these long-term results were indeed reassuring, however, one has to bear in mind that treatment had been discontinued [59]. Thus, the long-term data reflect the outcome of a long-term follow up, while the drug exposure was relatively short.

***Eltrombopag in MDS***

Eltrombopag is an agonist of thrombopoietin receptor which promotes growth and differentiation of megakaryocytes. Since 2014, it was approved by FDA for treatment of aplastic anemia, stimulating production of platelets, RBC and leukocytes. In LR-MDS patients with thrombocytopenia, it has shown efficiency of 47% in terms of platelet responses, *versus* 3% in the placebo group (Oliva et al., 2017) [60].

The ASPIRE study (Part I) was an open-label, double-blind study of patients with advanced MDS treated for 8 weeks with Eltrombopag, and randomised at later terms [61]. Four patients of 17 achieved increased platelet counts following treatment, and ten had reduced platelet transfusion requirements. Serious adverse events were reported in 58% of eltrombopag-treated, and in 68% placebo-treated patients. In ASPIRE II, fewer adverse events were registered.

Combined effects of Eltrombopag and Azacytidin (AZA) were addressed in the SUPPORT Study [62]. The intermediate-1, intermediate-2, or high-risk MDS patients with low platelet counts were randomized 1:1 to eltrombopag, or placebo, plus azacitidine. The development of this study was, however, stopped due to efficacy outcomes, and for safety problems.

The French MDS group (GFM) have recently presented their experience using long-term eltrombopag, with encouraging clinical efficacy. These promising data might assist in lifting the embargo on thrombomimetic agnets [63].

## Immunosuppressive therapy

Despite broad arsenal of novel therapeutic agents for MDS therapy, there are many LR-MDS patients with anemia who

are resistant or have lost their response to such drugs. Therefore, immunosuppressive treatment (IST) in these cases is well justified, on the basis of similarity between severe aplastic anemia and hypoplastic MDS. Some experience in this field exists with ATG and/or cyclosporine treatment [64]. Clinical response, however, is dependent on the MDS patient's age, transfusion history, and karyotype pattern, with erythroid response rate of 25-40%.

A large study published by Stahl et al. reported results of IST results obtained for cohort from 15 centers in Europe and USA, including 207 pts with MDS receiving IST [65].

The most common IST regimen was anti-thymocyte globulin (ATG) plus prednisone (43%). The overall response rate ORR 48.8%, with 11% reaching complete remission, and transfusion independence (RBC-TI) in 30% of the cases. Median overall survival (OS) was 47.4 mo, being longer for the patients with transfusion independence. The RBC-TI was associated with a bone marrow hypocellularity (<20%). Age, HLA-DR15 positivity did not predict clinical response to IST.

### Iron Overload

Iron deposition in the patients occurs due to intrinsic mechanisms of MDS, and as a result of multiple RBC transfusion, causing damage of liver and other organs.

Iron chelator therapy is effective in these cases. A retrospective study based on the European MDS Registry data was recently published by Hoeks et al. [66]. The results of chelator treatment in MDS were compared with non-chelated patients. The propensity-score analysis has revealed improved OS for chelated patients, with erythroid response in up to 39% of the treated cohort. A similar TELESTO study (the only prospective) included 225 patients with high serum ferritin levels after multiple RBC transfusions treated with Deferasirox [67]. Following continuous treatment (0.5 to 3 years), median EFS was prolonged by ca. 1 year (1440 d *vs* 1091 d) with deferasirox *vs* placebo, at 36% reduction of events.

Several eligibility criteria are proposed for initiating the chelator therapy [14, 68] (Mittelman et al., 2008, current Guidelines 2019; MDS-EUROPE online [14]: 1. Patients classified as low or Int1, according to the International Prognostic Scoring System; 2. Patients with serum ferritin levels >1000 μg/Ll and those who received a total of 20-25 RBC units; 3. Patients whose blood transfusion requirement has increased significantly; 4. Patients with sufficient organ damage.

## Summary and future prospects

Current treatment of the low-risk MDS includes the following:

- ESA +/- RBC transfusions;
- Lenalidomide (del 5q);
- 2nd Line:
  - Luspatercept; Roxadustat; Imetelstat; HMA (?)

Future prospectives:

- Combinations: ESA + other hematopoiesis-stimulating drugs;
- Novel agents;
- Low platelet counts in MDS patients:
  - Therapeutic approaches are still challenging.

## Conflict of interest

Disclosures: Research funding: Celgene; Johnson & Johnson; Roche; Novartis; Gilead. Speakers' bureau: Celgene; Johnson & Johnson; Novartis. Advisory boards (non-paid): Pfizer; Amgen; Roche; Novartis.

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# Миелодиспластический синдром (МДС) низкой степени риска: подходы к терапии без трансплантации

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## Резюме

За последние десятилетия достигнут значительный прогресс в понимании биологии и лечении миелодиспластических синдромов (МДС). На основе нескольких клинико-лабораторных параметров (процент бластных клеток, цитогенетические данные, число нарушенных ростков кроветворения) таких пациентов классифицируют по степени риска заболевания (сниженный или высокий риск). Здесь мы обратим особое внимание на МДС низкого риска (НР-МДС). Пациентов с НР-МДС лечат посредством трансфузий эритроцитов (при необходимости), с применением эритропоэз-стимулирующих препаратов или без них. Луспатерсепт, активирующий аналог, является рациональным препаратом для второй линии терапии. Среди изучаемых препаратов в этой области можно упомянуть руксодустат (ингибитор фактора, идуцируемого гипоксией) и имителстат – ингибитор геломеразы. Лечение тромбоцитопении остается проблемным и открытым вопросом.

## Ключевые слова

Миелодиспластический синдром, низкая степень риска, диагностика, лечение, таргетная терапия.