



## Guidelines

# Part 4: Myelodysplastic syndromes—Treatment of low-risk patients with the 5q deletion



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## PICO system

Using the PICO system, the P corresponds to patients with low-risk myelodysplastic syndrome with del(5q), I to the indication of treatments of interest, and the O to the outcome (prognosis).

Thus, 16 studies were found and selected to answer the clinical question ([Appendix I](#)).

**Objective:** The objective of these guidelines is to evaluate the treatment of low-risk myelodysplastic syndromes with the 5q deletion.

What treatments exist for low-risk myelodysplastic syndromes with the 5q deletion?

## Introduction

According to the International Prognostic Score System (IPSS) and, more recently, the revised IPSS (IPSS-R), myelodysplastic syndromes (MDS) are grouped into low risk (very low, low and intermediate) and high risk (high and very high). Anemia is predominantly a result of ineffective erythropoiesis, with excessive apoptosis being the hallmark of the disease in its early stages. Cytopenias, especially anemia, are the main problem in low-risk patients and have a well-established negative impact on morbidity, mortality and quality of life<sup>1</sup> (D).

## Low-risk MDS with the 5q deletion

MDS associated with an isolated deletion in the long arm of chromosome 5 [del(5q)] is considered to have a good prognosis when compared to the other subgroups of MDS, with a low probability of progression to secondary AML and longer life expectancy (>30 months). MDS with isolated del(5q) is the only defined cytogenetic category recognized in the 2001 and 2008

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classifications and in the 2016 revision of the World Health Organization (WHO)<sup>1</sup> (D).

Data from 84 patients with low-risk MDS (according to the IPSS and IPSS-R criteria) and del(5q) with no history of transfusion dependence were analyzed retrospectively. During the study period, 61 patients (73%) became transfusion dependent on average 1.7 years after diagnosis. Several factors with a potential impact on transfusion dependence were studied using univariate analysis, but only hemoglobin level of <9 mg/dL was associated with lower transfusion-free survival ( $p$ -value = 0.008); this result was maintained when multivariate analysis was performed. Of the 61 patients with transfusion dependence, 49 received other types of treatment (19 received lenalidomide, 24 received erythropoietin and six received other therapies). The estimated survival at 2 and 5 years was 92 and 50%, respectively. Platelet count <math>100 \times 10^9 L^{-1}</math> and intermediate IPSS-R risk were associated with worse outcomes while patients receiving any treatment had increased survival. This benefit was most evident in patients receiving lenalidomide with the mean overall survival (OS) not being reached by the end of the study (OS: 69 months for patients receiving erythropoietin and 24 months for patients without treatment)<sup>2</sup> (B).

### Erythropoiesis-stimulating agents

Several meta-analyses have evaluated the effect of erythropoiesis-stimulating agents in patients with low-risk MDS. Response rates range from 27 to 57% in patients with treatment duration >20 weeks treated at higher doses (60 000 U/week). Although the use of lenalidomide is considered the first line treatment for patients with del(5q), previous treatment with an erythropoiesis-stimulating agent is justified, mainly due to the high cost of lenalidomide and the difficulty of access to the drug<sup>3,4</sup> (A).

#### Thalidomide

The use of thalidomide at a dose of 50–100 mg/day for patients with MDS produced better results in younger patients with low-risk disease, a shorter evolution time and anemia as the only cytopenia. The response rate is limited to the erythroid series and ranges from 16 to 56% when intention-to-treat analysis is performed and between 31 and 88% when considering only those patients who received the drug for an appropriate period of time (at least 3 months)<sup>5</sup> (A). The frequency of adverse events limits tolerability. With the arrival of thalidomide analogs with significantly higher activity and minimal toxicity, studies mainly consider the use of lenalidomide for patients with del(5q). However, the use of thalidomide for patients with del(5q) is not recognized by any of the major international guidelines: National Comprehensive Cancer Network<sup>6</sup> (D), the European LeukemiaNet<sup>7</sup> (D) or the European Society for Medical Oncology<sup>8</sup> (D).

#### Lenalidomide

Lenalidomide is a second-generation immunomodulatory agent with multiple mechanisms of action acting

directly on MDS clones with reconstitution of erythropoietic immunomodulation and angiogenesis. It is more potent and has a more favorable activity/toxicity profile than thalidomide.

In the study that served as the basis for the Food and Drug Administration (FDA) approval of lenalidomide, 43 patients with MDS and symptomatic anemia were treated with lenalidomide 25 or 10 mg/day, or 10 mg/day for 21 days every 28 days. The response rate was significantly higher in patients with del(5q) (83%) when compared to patients with normal karyotypes (57%) and other chromosomal abnormalities (12%) ( $p$ -value = 0.007)<sup>9</sup> (B).

One hundred and forty-eight patients with MDS associated with del(5q) were treated with 10 mg of lenalidomide for 21 days every 4 weeks and subsequently monitored for 24 weeks; hematological and cytogenetic responses were analyzed by intention to treat. One hundred and twelve patients had reduced transfusion requirements and 67% became transfusion-free. The median response time was 4.6 weeks. Of the 85 patients analyzed, 73% presented cytogenetic improvements and of these, 61% presented complete remission. Moderate to severe neutropenia and thrombocytopenia were the most common adverse events<sup>10</sup> (B).

One hundred and sixty-seven patients with transfusion-dependent MDS were evaluated using the Health-Related Quality of Life questionnaire (HRQL) with the outcomes being assessed using the Functional Assessment of Cancer Therapy-Anemia (FACT-An). At 12 weeks of treatment, the FACT-An score was significantly higher in the group receiving lenalidomide (5 or 10 mg) than in the placebo group ( $p$ -value < 0.05). The percentage of patients with improvements according to the FACT-An score at 12 weeks was higher in the group receiving lenalidomide (5 mg—43.2% and 10 mg—47.9%) than in the Placebo Group (26%;  $p$ -value = 0.06). In patients who remained in the double-blind treatment for >48 weeks, the percentages of individuals with improvements according to the FACT-An score were 48–74 and 79–91% for those who received 5 and 10 mg lenalidomide, respectively<sup>4</sup> (A).

The efficacy and safety of lenalidomide was evaluated in a randomized phase III study of 205 MDS patients with del(5q) and low to intermediate IPSS risk who were dependent on transfusions. Doses of 10 mg/day were administered on days 1–21 ( $n$  = 69) or 5 mg/day on days 1–28 ( $n$  = 69) in 28-day cycles or placebo ( $n$  = 67). After 26 weeks, the proportions of transfusion-independent patients were 56.1, 42.6 and 5.9% for the 10 mg, 5 mg and placebo groups, respectively, with statistically significant differences for the groups receiving lenalidomide. Of the 45 patients receiving lenalidomide with erythropoietin levels >500 mLU/mL, transfusion independence was significantly higher for those who received 10 mg doses compared to 5 mg doses (76.2% vs. 33.3%;  $p$ -value < 0.004). Cytogenetic response rates (complete and partial) were 50.0% (10 mg) versus 25.0% (5 mg;  $p$ -value = 0.066). The complete cytogenetic response rates were 29.4 and 15.6% for 10 and 5 mg doses, respectively ( $p$ -value = 0.29). No cytogenetic response occurred in the placebo group ( $p$ -value < 0.001 in respect to the two lenalidomide groups). At 12 weeks, there was a significant increase in the quality of life evaluated using the FACT-An score in the groups receiving lenalidomide 10 and 5 mg vs. placebo. In the groups receiving lenalidomide, transfusion independence was associated with a 42% reduction in the

relative risk of progression to AML ( $p$ -value=0.048) and a 47% reduction in relative risk of death ( $p$ -value=0.021). The most common adverse events (Grades 3 and 4) were myelosuppression and deep venous thrombosis. Neutropenia and thrombocytopenia (Grades 3 and 4) usually occurred in the first two cycles and subsequently reduced. The incidence of adverse events was similar at both doses of lenalidomide<sup>11</sup> (A).

A meta-analysis of 17 studies involving 2160 patients with low-risk MDS with and without del(5q) showed that lenalidomide significantly improved OS (hazard ratio: 0.62; 95% confidence interval: 0.47–0.83;  $p$ -value=0.001) and decreased the risk of progression to acute leukemia in patients with del(5q) (relative risk: 0.61; 95% confidence interval: 0.41–0.91;  $p$ -value=0.014). The conclusion was that despite the profile of adverse events, lenalidomide is safe and effective for this group of patients. Studies evaluating the association of lenalidomide with other drugs such as erythropoietin or azacitidine have not shown any advantage in these combined treatments<sup>12</sup> (A).

A cooperative study involving 541 patients analyzed prognostic factors for OS and risk of progression to acute leukemia in patients with MDS and del(5q). The multivariate analysis showed that the most important predictors of survival and progression were cytogenetic abnormalities ( $p$ -value=0.001 for both), platelet count ( $p$ <0.001 and  $p$ -value=0.001, respectively) and percentage of blasts ( $p$ -value<0.001 and  $p$ -value=0.016, respectively). Two groups were defined for OS: the first group of del(5q) and del(5q) plus one cytogenetic alteration and the second group of del(5q) and two or more cytogenetic alterations; the mean OS was 58.0 and 6.8 months, respectively<sup>13</sup> (B).

The somatic mutation of the TP53 gene is one of the most common changes in human cancer. In MDS, it is described mainly in high-risk groups and is associated with complex karyotypes, changes in chromosome 17 and del(5q). In two different studies, the incidence of the TP53 mutation in the low-risk group with isolated del(5q) was 19 and 18%<sup>13,14</sup> (B). This percentage rises to 72% in patients with complex karyotypes associated with -5/5q-<sup>14</sup> (B). The presence of this mutation is associated with worse OS and progression-free survival with an important impact on decision-making<sup>15-17</sup> (B). In reviewing the WHO classification<sup>2</sup> (B), an investigation of the TP53 mutation is recommended in patients with MDS and isolated del(5q) to identify the subgroup of patients with worse prognosis.

## Recommendations

Lenalidomide at a dose of 10 mg daily for 21 days every 4 weeks is well tolerated, with a good safety profile (if creatinine clearance is >50 mL/min). This approach benefits independence from transfusions, cytogenetic response and quality of life in patients with low-risk/intermediate-risk MDS with del(5q) who are transfusion dependent and are not responsive to erythropoietin therapy. Erythropoiesis-stimulating agents can be used if lenalidomide is unavailable.

## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Appendix I

### 1. Clinical question

What treatments exist for low-risk MDS with the del(5q)?

### 2. Structured question (PICO)

Patients with low-risk MDS and the del(5q)

Intervention Lenalidomide

Erythropoietin-stimulating agents (erythropoietin, darbopoetin alone or in combination with G-CSF)

Thalidomide

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), relevance and applicability (Oxford/GRADE).<sup>18,19</sup>

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