with poor prognosis. While the other showed that the low *EZH2* expression is associated with alterations in chromosome 7 and disease progression. In our study, we observed that the *EZH2* overexpression in adult patients with MDS was associated with abnormal karyotipes and leukemic evolution. **Conclusion:** Our study suggests that *EZH2* overexpression is associated with the evolution from MDS to AML, being a possible prognostic biomarker. **Support:** Ministério da Saúde – INCA.

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IS FERRITIN A GOOD PREDICTOR OF SURVIVAL ACROSS ALL RISK LEVELS IN MYELODYSPLASTIC NEOPLASMS? INSIGHTS FROM A STRATIFIED COHORT STUDY

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Introduction: Myelodysplastic neoplasms (MDS) are a heterogeneous group of hematologic malignancies characterized by ineffective hematopoiesis. The Revised International Prognostic Scoring System (IPSS-R) is widely used to stratify MDS patients into different risk categories, guiding treatment decisions and predicting survival outcomes. Ferritin has been implicated in the pathophysiology of MDS. Elevated ferritin levels may reflect iron overload, inflammation, or both. However, the prognostic value of ferritin across different risk levels in MDS remains unclear. **Objective:** This study aims to evaluate the prognostic significance of ferritin in patients with MDS, stratified by IPSS-R risk categories. **Methods:** A retrospective cohort study at a single reference center reviewed patients diagnosed with MDS between 2004 and 2024. The study included patients with available clinical outcomes and ferritin values. Missing data for other variables were addressed using the classification and regression tree analysis (CART) Multiple imputation method, following confirmation of non-completely at random missingness through Little's test. Patients were stratified into two groups based on IPSS-R scores: 'high risk', comprising those categorized as 'High' or 'Very High', and 'low risk', encompassing all other IPSS-R categories. The CART method was utilized to determine the optimal ferritin cut-off for predicting overall survival, applying Martingale residuals from a univariate Cox model adjusted for ferritin. Kaplan-Meier curves were subsequently generated to assess survival rates at 1, 3, and 5 years post-diagnosis for patients below and above the ferritin cut-off, with comparisons conducted using log-rank tests. All statistical analyses were performed using R software, leveraging the 'mice' package for imputation and the 'survfit' package for survival analysis. **Results:** A total of 143 patients with available ferritin values and clinical outcomes were included in the study. Using the CART method, an optimal ferritin cut-off of 888.5 was determined, classifying the cohorts into "High Ferritin" (32 patients) and "Low Ferritin" (111 patients). Kaplan-Meier 1, 3, and 5-year survival curves were constructed for both the 'high risk' (17 patients) and 'low risk' (126 patients) groups. Among the 'low risk' patients, those with low ferritin levels, compared to those with high ferritin levels, had significantly higher 3 (78.6% vs 44.3%, $p < 0.001$) and 5-year (57.3% vs. 34.8%, $p < 0.001$) survival rates, although no difference was seen in 1-year rates ($p = 0.45$). Within the 'high risk' group, no difference between the high and low ferritin groups was seen in 1, 3, or 5-year survival rates ($p = 0.26$, 0.066, and 0.066, respectively). **Discussion:** Ferritin, a marker of iron overload and inflammation, plays a role in the pathophysiology of MDS. Our study shows that ferritin levels predict long-term survival in low-risk MDS patients, consistent with previous studies, but are less predictive in high-risk patients. This suggests ferritin's impact may be overshadowed by other factors in high-risk MDS. **Conclusion:** Ferritin level at diagnosis is a good predictor of long-term survival for non-high risk MDS patients, but its efficacy in predicting outcomes for high-risk patients and general short-term survival is less evident.

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STRENGTHENING THE EVIDENCE: RAP1B GENE ASSOCIATION WITH SYNDROMIC THROMBOCYTOPENIA

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Introduction: Syndromic thrombocytopenia encompasses a heterogeneous group of disorders characterized by both quantitative and qualitative defects of platelets, often accompanied by other malformations. The clinical manifestations of patients vary in severity, but bleeding is considered the main complication, which can lead to the development of other disorders such as hematological malignancies. Recently, heterozygous, *de novo* variants in *RAP1B* have been reported in five cases of syndromic thrombocytopenia. Here, we report an additional case of syndromic thrombocytopenia associated with a rare *de novo* variant in *RAP1B*. **Case:** We present a case of a 2-year-old female patient with thrombocytopenia first observed at the age of 6 months. She has severe, persistent thrombocytopenia that is refractory to various therapies. The main phenotypic characteristics identified were hypertelorism, low ear implantation, and a broad forehead. Exome sequencing revealed a rare *de novo* heterozygous variant in the *RAP1B* gene (NM_001010942.3 c.178G>A p.

(Gly60Arg)), classified as likely pathogenic. **Discussion:** The *RAP1B* gene (OMIM: 179530) is associated with the clinical phenotype of syndromic constitutional thrombocytopenia. Currently, only a few genotype-phenotype associations have been described in the literature. The previously reported variants include c.35G>T (p.Gly12Val), c.176C>G (p.Ala59Gly), c.178G>C (p.Gly60Arg), c.35G>A (p.Gly12Glu), and c.178G>A (p.Gly60Arg). RAP1B is a member of the RAS superfamily of small GTPases involved in many cellular processes. Previous studies have shown a link between RAP1B activation and platelet function in humans and mice. Our case report shares the common phenotype of thrombocytopenia (HP: 0001873), suggesting the clinical relevance of this phenotype to variants in this region of the *RAP1B* gene. Notably, 4 out of 5 (80%) described variants in public genomic databases are located in exon 4, indicating that this exon may be particularly relevant to the clinical condition. **Conclusion:** Our data support that the *RAP1B* variant detected in our patient may contribute to the phenotype through dysregulation of the MEK/ERK pathway. The effects of variants in *RAP1B* explain the divergent phenotypes observed among patients. Nonetheless, further studies are required to understand better the correlation between genotype and phenotype.

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LONG-TERM EFFECTIVENESS AND SAFETY OF LUSPATERCEPT FOR ANEMIA TREATMENT IN PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Erythropoiesis-stimulating agents (ESA) are the primary treatment for anemia in most patients with low to moderate-risk myelodysplastic syndromes. However, in some patients, ESA therapy is not effective, and emerging evidence suggests that Luspatercept may offer longstanding benefits in these patients. **Objective:** This study evaluated the long-term effectiveness and safety of luspatercept in treating anemia in patients with low-risk syndrome (MDS). It focused on achieving at least eight weeks of red blood cell transfusion independence and examined hematologic responses, particularly in relation to erythroid ring sideroblasts. **Methods:** We searched MEDLINE, Embase, and Cochrane databases for Clinical trials (CT) that assessed events of effectiveness and safety with the use of Luspatercept in patients with Low-risk Myelodysplastic Syndrome from inception to July 2024. Following the PRISMA protocol, 688 articles were screened. The primary endpoints focused on red blood cell transfusion independence for at least 8, as well as hematologic response-erythroid. Adverse events such as bone pain were also pooled and analyzed. We calculated event prevalence for binary outcomes, along with 95% confidence intervals (CI). A random-effects model was used for all outcomes, and heterogeneity was assessed with I2 statistics. **Results:** After duplicate removal and exclusion by title and abstract, 12 studies were thoroughly read, and 5 articles referring to 3 CT, encompassing 393 patients treated with luspatercept that were enrolled and evaluated in this meta-analysis. All the groups had similar demographics and clinical factors. The mean age was 72.5 years, 273 (62.2%) were male and 196 (44.65%) were previously treated with real-world erythropoiesis-stimulating agents (ESA). Among all patients, SF3B1 mutations were detected in 296 (47.28%) patients, while 330 (52.72%) were positive for ring sideroblasts. Luspatercept was associated with a proportion of hematologic response-positive erythroid ring sideroblasts, accounting for 68.13% (95% CI 56.74 to 79.52; $p < 0.01$; $I^2 = 82\%$). In addition, the proportion of patients who were independent of red cell transfusion for at least 8 weeks was 48.17% (95% CI 42.56 to 53.79; $p = 0.55$; $I^2 = 0\%$). In patients with SF3B1 mutations, the proportion of hematologic response-positive erythroid was 48.73% (95% CI 42.32 to 55.14; $p < 0.43$; $I^2 = 0\%$), and the proportion of patients who were independent of red-cell transfusion for at least 8 weeks was also 48.73% (95% CI 42.32 to 55.14; $p = 0.43$; $I^2 = 0\%$). The proportion of bone pain was 3.87% (95% CI 1.56 to 9.28; $p < 0.09$; $I^2 = 58\%$) among all patients. **Discussion:** This meta-analysis identified a significant link between luspatercept use and a positive hematologic response in erythroid ring sideroblasts, indicating notable anemia improvement in many patients. Nearly half achieved at least 8 weeks of red blood cell transfusion independence, demonstrating significant clinical benefit. Among patients with SF3B1 mutations, the hematologic response rate was slightly lower but matched the transfusion independence rate, indicating consistent efficacy across this genetic subgroup. The study also noted a low incidence of bone pain, a common adverse effect in many hematologic treatments. This low incidence, combined with the efficacy data, suggests a favorable safety profile for luspatercept. **Conclusion:** Luspatercept seems to be associated with improved hematological parameters while having a small prevalence of adverse outcomes. However, more clinical trials are necessary to completely assess its use in the long term and in comparison with other interventions.

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