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Hematological adverse effects of Imetelstat in Patients with Myelodysplastic Syndromes

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Abstract

Background: Imetelstat, is effective in treating myelodysplastic syndromes (MDS) but is associated with hematological adverse effects.
Objective: To assess hematological adverse effects of Imetelstat and to evaluate imetelstat as an effective therapy option for individuals with MDS
Methodology: An electronic search from PubMed/Medline, Cochrane Trial register and Google scholar was conducted from their inception to 20th June 2024. OpenMeta[Analyst] software was used for all statistical analyses. Random effects models were used to calculate the pooled incidence measures and the corresponding 95% confidence intervals (CI).
Results: Four studies, with a total of 353 participants, were selected for analysis. The incidence of thrombocytopenia in patients using Imetelstat across the 4 studies reporting on 353 patients ranged from 22.9% to 65.8%. The overall pooled incidence of thrombocytopenia was 50.4% (95% CI 37.7% - 63.2%). The incidence of neutropenia in patients using Imetelstat across the 3 studies reporting on 246 patients ranged from 15.8% to 67.8%. The overall pooled incidence of neutropenia was 51.2% (95% CI 32.8% - 69.6%). The incidence of anemia in patients using Imetelstat across the 3 studies reporting on 235 patients ranged from 22.8% to 44.1%. The overall pooled incidence of anemia was 32.3% (95% CI 24.7% - 39.9%).
Conclusion: Despite imetelstat has mild hematological side effects, it shows promise in treating myelodysplastic syndromes (MDS), as the adverse effects are manageable. Imetelstat's advantages for treating MDS patients outweigh the hazards of thrombocytopenia, neutropenia, and anemia, hence enabling its usage in clinical practice.
Keywords: Imetelstat; Telomerase inhibitor; Myelodysplastic syndromes; Meta-analysis

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Introduction

The bone marrow neoplasm referred to as myelodysplastic syndrome (MDS) is caused by clonal hematopoietic dysfunction, which impairs hematopoiesis and causes bone marrow cell dysplasia and peripheral cytopenias.[1] The incidence of MDS in the United States is about 4.9 per 100,000 people yearly; rates increase with age, especially in those over 80; males and Caucasians are more likely to be affected.[2] MDS is a multifactorial disorder, that can be caused by a variety of somatic and germline mutations, according to research.[3] A potential factor contributing to MDS is overexpression of human telomerase reverse transcriptase (hTERT), which promotes telomerase activity.[4]

Telomeres, which are non-coding repetitive sequences of nitrogenous bases (5'-TTAGGG-3' in humans) present at the end of DNA, are essential for maintaining the stability and integrity of chromosomes because they shield DNA from damage, degradation, and fusion with nearby chromosomes. Telomeres usually shorten with each cell division; this progressive shortening acts as a biological clock to limit the number of cell divisions that a cell can undergo.[5] Telomerase, a ribonucleoprotein reverse transcriptase enzyme responsible for maintaining the telomere length with each cell division. It does so by using its RNA component as a template to builds new telomeric DNA sequence at the end of chromosome [5,6]. Telomerase activity is low in normal somatic cells, which causes the cells to die naturally with age. However, telomerase activity is elevated in malignancies and myelodysplastic syndromes, which allows aberrant cells to survive longer and avoid senescence.[4,7]

Tightly targeting the human telomerase RNA template, Imetelstatis a 13-mer oligonucleotide that is a very effective, first-in-class competitive inhibitor of telomerase enzymatic activity.[8] Imetelstat has been demonstrated to block telomerase activity in a variety of cancer cell lines and myelodysplastic syndromes.[9,10] Imetelstat's safety profile, particularly its hematological side effects,

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continues to raise concerns, despite its promising efficacy as a telomerase inhibitor in treating myelodysplastic syndromes.[11]

To ascertain if this could be a useful therapeutic alternative, our study is to assess the frequency of hematological side effects in patients with myelodysplastic syndromes. Our research aims to maximize treatment choices for MDS patients and educate evidence-based clinical practice by examining the hematological side effects of imetelstat. This could possibly expand therapeutic alternatives while addressing current therapy limits. To determine if imetelstat can be a successful treatment for this challenging condition, this study intends to investigate the therapeutic potential of imetelstat in the setting of MDS.

Methodology

Data sources and search strategy: This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta analyses (PRISMA) guidelines.[12] An electronic search from PubMed/Medline, Cochrane Trial register and Google scholar was conducted from their inception to 20th June 2024, using the search string (Imetelstat) AND (Adverse effects OR Adverse events) AND (Myelodysplastic Syndrome OR MDS OR Myelofibrosis). In addition, we manually screened the cited articles of previous meta-analyses, cohort studies, and review articles to identify any relevant studies.

Study selection: All studies were included if they met the following eligibility criteria described as PICOS: P (Population/Patients); Myelodysplastic syndrome patients or Myelofibrosis patients; I (Intervention) Imetelstat therapy; O (Outcome) Hematological adverse effects; S (Studies) Clinical Trials published in English language.

Data extraction: Two Reviewers independently searched electronic databases. Studies searched were exported to the EndNote Reference Library software version 20.0.1 (Clarivate Analytics) and duplicates were screened and removed. The investigators extracted data entering them on a computer spreadsheet. Discrepancies were resolved through consensus discussions among investigators. The following data were extracted from each eligible study: first author's name, year of publication, location of study, date of study and sample size.

Quality assessment of studies: Quality of each of the included studies was assessed. The risk of bias was assessed through Modified Cowley's criteria.[13] Each of the 13 entities is scored as 2: satisfactory reporting, 1: partial reporting, 0: no reporting. The individual domains and overall risk-of-bias judgement were expressed on one of three levels: low risk of bias (score 24–26/26), moderate risk of bias (score 20–23/26), and high risk of bias (score < 20/26) (Table I).

Statistical analysis: OpenMeta[Analyst] software was used for all statistical analyses.[14] Random effects models were used to calculate the pooled incidence measures and the corresponding 95% confidence intervals (CI).

Table I: Modified Cowley's criteria scoring for risk-of-bias assessment.

	Tefferi A et al.	Mascarenhas J et al.	Steensma DP et al.	Platzbecker U et al.
Method of selection of patients identified and appropriate	2	1	2	2
Number of patients deceased or lost to follow-up are either reported or included in appropriate statistical analysis	2	2	2	2
Follow-up period, range and mean mentioned	2	2	2	2
Scaffold/stent models specified (or interventional strategy)	2	2	2	2
Well-defined criteria for outcomes measurement	2	1	2	2
Valid statistical analysis undertaken	1	1	1	2
Data mentioned for deceased individuals	0	1	2	0
Age range and mean age stated	2	2	1	2
Type of lesion stated	2	2	2	2
Pre-operative diagnosis and percentages of patients given	2	2	2	2
Quantification of outcomes	2	2	2	2
Clinical outcomes reported at follow-up	2	2	2	2
Independence of investigators (no conflict of interest)	2	2	2	2
TOTAL SCORE	23	22	24	24

**each entity is scored as 2: satisfactory reporting, 1: partial reporting, 0: no reporting*

The heterogeneity of the findings was assessed using both the Cochran's Q test and the I^2 statistic. Sensitivity analysis was done to see if any individual study was driving the results and to implore reasons of high heterogeneity. As per Cochrane handbook, scale for heterogeneity was considered as follows: I^2 = 25–50% – moderate; 50–75% – substantial; 75–100% – considerable heterogeneity, and p< 0.1 indicated significant heterogeneity. A p< 0.05 was considered significant for all analyses.

Results

Literature search results: The initial search of the three electronic databases yielded 127 potential studies. After exclusions based on titles and abstracts, the full text of 13 studies was read for possible inclusion. A total of 4 studies remained for qualitative and quantitative analysis.[8,10,15,16] Figure 1 summarizes the results of our literature search.

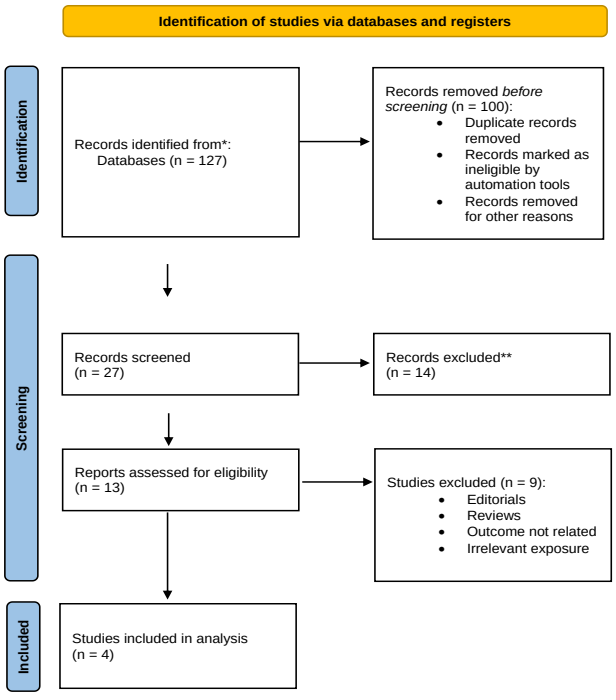

Figure 1. Literature search strategy.

Study characteristics: Four studies evaluated a total of 353 participants using the drug (Table II).[8,10,15,16]

Publication bias and quality assessment: There were less than 10 studies so publication bias could not be assessed. Out of the 4 studies, 2 had low risk of bias [10,15] and 2 had moderate risk of bias.[8,16]

Results of Meta-Analysis: Detailed forest plots, outlining the pooled estimates of overall incidences of thrombocytopenia, neutropenia and anemia are shown in Figures 2-4

Incidence of Thrombocytopenia: The incidence of thrombocytopenia in patients using Imetelstat across the 4 studies. reporting on 353 patients ranged from 22.9% to 65.8%.[8,10,15,16] The overall pooled incidence of thrombocytopenia was 50.4% (95% CI 37.7% - 63.2%) and there was a considerable heterogeneity (I^2 = 82.86%, P< 0.001) between the estimates (Figure 2).

Incidence of Neutropenia: The incidence of neutropenia in patients using Imetelstat across the 3 studies reporting on 246 patients ranged from 15.8% to 67.8%.[10,15,16] The overall pooled incidence of neutropenia was 51.2% (95% CI 32.8% - 69.6%) and there was a considerable heterogeneity (I^2 = 88.18%, P< 0.001) between the estimates (Figure 3).

Incidence of Anemia: The incidence of anemia in patients using Imetelstat across the 3 studies [8,15,16] reporting on 235 patients ranged from 22.8% to 44.1%. The overall pooled incidence of anemia was 32.3% (95% CI 24.7% - 39.9%) and there was a moderate heterogeneity (I^2= 35.37%, P = 0.171) between the estimates (Figure 4).

Non-Hematological adverse effects: Overall, our studies indicated that while there were notable non-hematological adverse effects, the most significant findings included mild elevations in hepatic enzyme levels. These included total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. However, these enzyme level alterations did not result in overt hepatic damage, and in the majority of cases, the levels returned to baseline.[8,15,16]

Other adverse effects reported across multiple studies included nausea, fatigue, diarrhea, and asthenia.[8,15,16] Two studies specifically noted instances of peripheral edema. [8,15] Additionally, several rare adverse effects were documented by individual studies, including dyspnea.[8], abdominal pain, epistaxis, back pain, headache, bronchitis and nasopharyngitis.[8,15,16] Tefferi also reported cases of lung infections, skin infections, and upper gastrointestinal hemorrhage.[16]

Effectiveness: Among all the studies, the effectiveness of the drug was consistent. Major positive outcomes achieved included complete or partial remission,

Table II: Basic characteristics of selected articles.

Study	Study year	Study design	Study period	Study location	Total patients evaluated (n)	Age (years)	Risk of bias
Tefferi A et al.	2015	clinical trial	2012-2014	USA, Canada, France, Germany, Spain and others	33	≥18	Moderate
Mascaren-has J et al.	2021	clinical trial	2015-2016	US, Canada, Germany, France, UK and others	107	≥18	Moderate
Steensma DP et al.	2020	clinical trial	2015-2023	USA	57	≥18	Low
Platzbe-cker U et al.	2023	clinical trial	2019-2021	17 countries	118	≥18	Low

considerable transfusion independence[15,10] and reversal of bone marrow fibrosis.[16,8] Variant allele frequency reduction of driver mutations, and reduction of telomerase activity and human telomerase reverse transcriptase levels were also observed, which correlated with symptom response, spleen response and overall survival.[8] Moreover, disease modification activity was suggested by a reduction in malignant clones as revealed through cytogenetic and mutational data.[15]

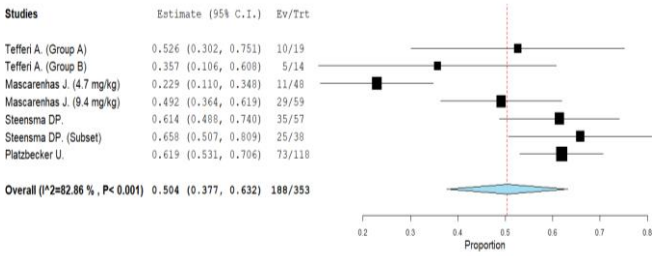

Figure 2. Forest plot of Thrombocytopenia.

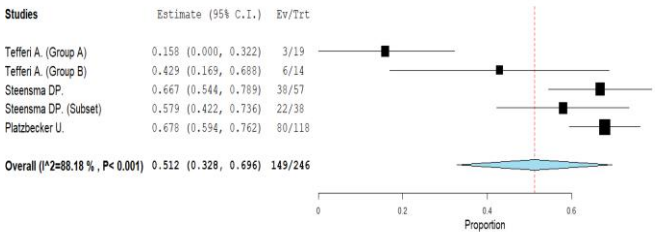

Figure 3. Forest plot of neutropenia.

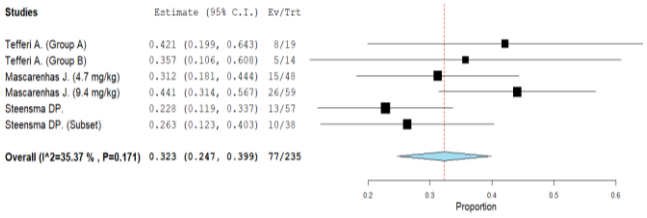

Figure 4. Forest plot of anemia.

Discussion

Myelodysplastic syndromes (MDS) may benefit from the use of imetelstat, a strong telomerase inhibitor, as a potentially effective treatment.[15] Hematopoiesis that is not effective and a tendency toward acute myeloid leukemia are the characteristics of these diseases.[1,17] Using a unique strategy, imetelstat inhibits the abnormal growth of cancerous cells in MDS by specifically targeting telomerase, an enzyme essential for preserving telomere length and cell immortalization.[16]

This study was conducted to delineate the potential adverse hematological outcomes of imetelstat use in patients with MDS and myelofibrosis. Our study demonstrates that the most prominent and frequently reported hematological adverse effects in imetelstat users are thrombocytopenia, neutropenia and anemia. However, majority of these hematological effects are reversible and manageable over time, and do not have long-term detrimental implications.

In the Masarenhas J trial, majority of the grade 3 and 4 neutropenia resolved within 4 weeks to grade ≤ 2. More than 70% of all thrombocytopenia also downgraded to grade 2 or below over a period of 4 weeks with limited clinical sequelae. Likewise, majority of neutropenia, anemia and thrombocytopenia occurring in Steensma and Platzbecker eventually resolved and had limited and tolerable clinical outcomes. As such, severe infections due to neutropenia, and significant hemorrhagic events due to thrombocytopenia did not occur, and no deaths were reported to occur due to the cytopenias.

The adverse effects were generally short-term and reversible which could be managed by delaying treatment and adjusting doses, enabling the patients to stay on treatment and continue to benefit clinically from the drug's use. This suggests that the drug's effectiveness is not compromised by these adverse effects.

It was assumed that imetelstat, being an oligonucleotide, can induce cytopenias especially thrombocytopenia through activation of Toll-like receptors. However, it was found that imetelstat treatment had no stimulatory effects

on Toll-like receptors since the drug's structure does not meet the structural requirements for activation of TLR. [18] Imetelstat can induce cytopenias by various mechanisms such as decreased production and increased destruction. Telomerase activity is essential for proliferation and survival of hematopoietic cells. Inhibition of telomerase by imetelstat inhibits cell production from hematopoietic stem cells. Moreover, imetelstat can shorten the lifespan of blood cells that can lead to premature destruction and removal of these cells from the circulation.[19] Imetelstat delays the maturation of hematological precursor cells and affects normal production of these cells.[20]

MDS patients who are treated with imetelstat the predominant off-target effects include the development of cytopenias. However, in the imerge 3 trial platzbacker clinical consequences of grade 3-4 infection or bleeding were similar in patients treated with imetelstat and placebo. Moreover, these treatment-emergent adverse effects are more prevalent in the initial cycles of the treatment, and the frequency decreases over time with subsequent treatment cycles.[11] The hematological adverse effects, even though mild, pose certain risks for the patients. These should be taken care of with vigilant monitoring and supportive measures. For example, regular monitoring of hemoglobin levels in anemic patients, watching out for bleeding events in patients with thrombocytopenia, and proactive management of infections and sepsis in patients with neutropenia.

Imetelstat has been approved by the FDA despite its side effects since clinical trials have shown it to be effective in treating MDS. The acceptable risks of anemia, thrombocytopenia, and neutropenia are surpassed by the advantages of imetelstat in terms of postponing the course of the disease and enhancing overall survival. Research is still being conducted to improve patient outcomes and guarantee the safe administration of imetelstat in MDS. Dosing techniques and supportive care regimens are being refined.

Conclusion

Despite imetelstat has mild hematological side effects, it shows promise in treating myelodysplastic syndromes (MDS), as the adverse effects are manageable. Imetelstat's advantages for treating MDS patients outweigh the hazards of thrombocytopenia, neutropenia, and anemia, hence enabling its usage in clinical practice.

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