Editorial

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# Imetelstat (Rytelo): a promising treatment for adults with lower-risk MDS and transfusion-dependent anemia

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Myelodysplastic syndromes (MDS) are classified as a group of cancers where the malignant cells present in bone marrow malfunction, producing inadequate red blood cells (RBC) and consequent anemia[1]. RBC transfusion dependency is common among people who have MDS of lower risk, and it is linked to both the short- and long-term clinical outcomes, which lowers the quality of life and shortens the survival rate for individuals[2]. On 6 June 2024, according to findings of the IMerge Phase 3 clinical trial, the Food and Drug Administration (FDA) approved Imetelstat in order to treat adult patients who have transfusion-dependent (TD) anemia, defined as those with low to about intermediate-risk MDS, requiring four or more RBC units over the course of 8 weeks, and who are not eligible for erythropoiesis-stimulating agents (ESA), the standard first-line treatment for anemia in MDS[3].

The PC-MDS cell line was derived from the bone marrow of a patient with therapy-related myelodysplastic syndrome (t-MDS), who had previously undergone treatment for acute lymphoblastic leukemia (ALL) with polychemotherapy. These cells exhibit a predominantly round or ovoid shape, with large nuclei and abundant cytoplasm, and they show a high mitotic index, indicating rapid proliferation. Immunophenotyping reveals that the cells express myeloid markers such as CD13, CD15, CD33, and CD45, as well as the activation marker CD30, while being negative for lymphoid markers, confirming their myeloid lineage. Cytogenetic analysis of the PC-MDS cell line shows complex chromosomal abnormalities commonly associated with MDS, including deletions and aneuploidy, with specific alterations like del(5q) and the loss of chromosome 7. Additionally, the cells exhibit hypermethylation of the MGMT gene promoter, though the p15 and p16 genes do not show such methylation, suggesting that different mechanisms may be involved in their inactivation. This cell line serves as a valuable model for studying the biological and molecular characteristics of MDS, particularly in relation to cytogenetic changes and methylation patterns[4].

Compared to other hematopoietic cells, MDS cells show a higher degree of necrosis and apoptosis, which indicate ineffective hematopoiesis, which results in peripheral cytopenia's despite the bone marrow often being hypercellular. This paradox is largely due to increased apoptosis and necrosis of hematopoietic cells within the marrow. In MDS, dysregulation of apoptotic pathways leads to an overexpression of pro-apoptotic factors, such as Fas and Bax, and a decrease in anti-apoptotic factors like Bcl-2, driving excessive cell death. This heightened apoptosis is particularly prominent in early-stage MDS, contributing to the failure of hematopoietic cells to mature and enter the bloodstream. As the disease progresses, apoptosis may decrease, correlating with a shift towards more aggressive forms of MDS and potential progression to acute myeloid leukemia (AML). Understanding these apoptotic mechanisms is crucial for developing targeted therapies aimed at modulating cell death in MDS[5].

The injectable oligonucleotide telomerase inhibitor Imetelstat is the first drug of its kind, as it functions by attaching to the telomerase enzyme, preventing telomere binding and blocking its activity. Treatment with Imetelstat causes cell death, shortens telomeres, and decreases the quantity of cancerous stem and progenitor cells[3]. Imetelstat acts especially on those cells with high telomerase activity—a common feature observed in malignant cells in MDS. Telomerase is an enzyme responsible for maintaining the length of the protective caps of telomeres on the chromosomes protecting DNA during cell division. In MDS, malignant hematopoietic stem and progenitor cells rely on telomerase to prevent apoptosis and to maintain uncontrolled proliferation. This process is disturbed by Imetelstat via its binding to the RNA template of the hTERC enzyme. Telomere elongation is prevented as a result, and this leads to the critical shortening of telomeres. These changes lead to DNA damage and cellular senescence, followed by apoptosis in MDS cells[6,7]. Furthermore, in the IMerge Phase 3 trial, evidence was provided that inhibition of telomerase by Imetelstat reduces mutational burden in MDS cells. In patients with prolonged transfusion independence, a reduction in VAF of the SF3B1 gene commonly mutated in MDS has been observed; this therefore suggests that

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Imetelstat, beyond addressing anemia, may have disease-modifying effects by targeting clonal hematopoiesis[8]. These molecular discoveries underscore Imetelstat's capacity to impact the course of MDS, setting it apart from other treatments that chiefly target anemia-related symptoms.

When compared to a placebo, Imetelstat was linked in clinical trials to a noticeably greater number of red blood cell transfusion independence (RBC-TI). Compared to 15% of placebo-treated individuals, 39.8% of Imetelstat-treated patients experienced at least 8 weeks of RBC-TI. The rates for Imetelstat came out to be 28%, while the rates for placebo were 3.3% for at least 24 weeks of RBC-TI. Its benefits also include durable and sustained RBC-TI, with a median duration of 1.5 years for those who responded for 24 weeks and 1 year for those who responded for 8 weeks[8]. Transfusion dependency is associated with iron overload, infections, and cardiovascular problems. Imetelstat can improve overall hemopoiesis and achieve sustained transfusion independence, which might contribute to a reduction in several comorbidities. Elevated telomerase activity in malignant clones is one of the hallmarks of MDS that Imetelstat targets. While blood transfusions are not a treatment for the underlying disease, Imetelstat may lead to disease modification and longer-term benefits through reductions in malignant clone burden[9]. One additional treatment option for such patients is the erythroid maturation agent Luspatercept, approved for the treatment of anemia due to myelodysplastic syndromes and some other hematologic disorders. Luspatercept's therapeutic activity appears to be limited to partial amelioration of anemia in a subset of patients with ring sideroblasts, having less of an overall impact. In contrast, Imetelstat exhibits efficacy and has the potential to modify disease[10] (Table 1).

With the approval of Imetelstat, there are some significant long-term effects that come into action with the approval of Imetelstat. One of which is the drug's distinct mode of action, which aims to inhibit the growth of malignant cells and cause them to die. This means that in addition to treating the symptoms of anemia, it also has the ability to modify the disease. The development of telomerase inhibitors in MDS and other hematologic malignancies may be facilitated by Imetelstat's success. Several clinical trials, including a critical Phase 3 trial in myelofibrosis and a Phase 3 trial in lower-risk MDS, are being investigated. Investigator-initiated trials are also evaluating the medication in high-risk MDS and acute myeloid leukemia[11]. The aim of these trials is to further assess Imetelstat's safety and effectiveness in relation to many different hematologic malignancies.

Although Imetelstat has indeed given promising results in achieving transfusion independence in lower-risk MDS patients, its limitations include significant adverse events such as thrombocytopenia and neutropenia, which could require dose adjustments or treatment pauses. There are also concerns about reproductive toxicity, mainly precluding its use in women of childbearing age. Long-term efficacy, in particular with respect to disease progression or resistance, is still under investigation[3]. The high cost of treatment could once again be a serious limitation in accessibility for certain patients. Despite all these setbacks, Imetelstat constitutes a breakthrough in the management of lower-risk MDS and transfusion-dependent anemia.

**Table 1**

**Overview of Imetelstat (Rytelo) for lower-risk MDS and transfusion-dependent anemia.**

| Category | Details |
|---|---|
| Disease | Myelodysplastic syndromes (MDS) are classified as a group of cancers where the malignant cells present in bone marrow malfunction, producing inadequate red blood cells (RBC) and consequent anemia[1]. RBC transfusion dependency is common among people who have MDS of lower-risk, and it is linked to both, the short as well as long-term clinical outcomes which lowers the quality of living and shortens the survival rate for individuals[2]. |
| FDA approval | On 6 June 2024, according to findings of IMerge Phase 3 clinical study, Food and Drug Administration (FDA) approved Imetelstat in order to treat adult patients who have transfusion-dependent (TD) anemia, defined as those with low to about intermediate-risk MDS, requiring four or more RBC units over the course of 8 weeks and who are not eligible for erythropoiesis-stimulating agents (ESA)—the standard first-line treatment for anemia in MDS[3]. |
| Drug | The injectable oligonucleotide telomerase inhibitor Imetelstat is the first drug of its kind, as it functions by attaching to the telomerase enzyme, preventing telomere binding and blocking its activity. Treatment with Imetelstat causes cell death, shortens telomeres, and decreases the quantity of cancerous stem and progenitor cells[3]. |
| Clinical results | When compared to a placebo, Imetelstat was linked in clinical trials to a noticeably greater number of red blood cell transfusion independence (RBC-TI). Compared to 15% of placebo-treated individuals, 39.8% of Imetelstat-treated patients experienced at least 8 weeks of RBC-TI. The rates for Imetelstat came out to be 28% while the rates for placebo were 3.3% for at least 24 weeks of RBC-TI. Its benefits also include durable and sustained RBC-TI, with a median duration of 1.5 years for those who responded for 24 weeks and 1 year for those who responded for 8 weeks[8]. |
| Benefits | Transfusion dependency is associated with iron overload, infections, and cardiovascular problems. Imetelstat can improve overall hematopoiesis and achieve sustained transfusion independence, which might contribute to a reduction in several comorbidities. An elevated telomerase activity in malignant clones is one of the hallmarks of MDS that Imetelstat targets. While blood transfusions are not a treatment for the underlying disease, Imetelstat may lead to disease modification and longer-term benefits through reductions in malignant clone burden[9]. |
| Comparative treatment | One additional treatment option for such patients is the erythroid maturation agent Luspatercept, approved for the treatment of anemia due to myelodysplastic syndromes and some other hematologic disorders. Luspatercept's therapeutic activity appears to be limited to partial amelioration of anemia in a subset of patients with ring sideroblasts, having less of an overall impact. In contrast, Imetelstat exhibits efficacy and has the potential to modify disease[10]. |
| Long-term effects | There are some significant long-term effects that come into action with the approval of Imetelstat. One of which is the drug's distinct mode of action, which aims to inhibit the growth of malignant cells and cause them to die. This means that in addition to treating the symptoms of anemia, it also has the ability to modify the disease. Development of telomerase inhibitors in MDS and other hematologic malignancies may be facilitated by Imetelstat's success. Several clinical trials, including a critical Phase 3 trial in Myelofibrosis and a Phase 3 trial in lower-risk MDS are being investigated. Investigator-initiated trials are also evaluating the medication in high-risk MDS and acute myeloid leukemia[11]. The aim of these trials is to further assess Imetelstat's safety and effectiveness in relation to many different hematologic malignancies. |
| Side effects and limitations | Although Imetelstat has indeed given promising results in achieving transfusion independence in lower-risk MDS patients, its limitations include significant adverse events such as thrombocytopenia and neutropenia, which could require dose adjustments or treatment pauses. There are also concerns about reproductive toxicity, mainly precluding its use in women of childbearing age. Long-term efficacy, in particular with respect to disease progression or resistance, is still under investigation[3]. |

## Ethical approval

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## Consent

As this is an editorial, ethical considerations regarding patient consent and privacy do not apply.

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## Author contribution

I.F.A.: conceptualization, writing—original draft. A.T.: writing—original draft. M.F.: writing—original draft. M.H.S.: supervision, writing—review and editing. F.G.: supervision, writing—review and editing. C.B.: supervision, writing—review and editing.

## Conflicts of interest disclosure

The authors declare no conflicts of interest.

## Research registration unique identifying number (UIN)

As this is an editorial without the involvement of human subjects, do not apply.

## Guarantor

All the authors certify to be the guarantor.

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The datasets generated and/or analyzed during the current study are not applicable. No data was generated or analyzed in this research project.

## Provenance and peer review

Not invited.

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