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Therapeutic impact of Telomerase Inhibitor Imetelstat: A Literature Review

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ABSTRACT Telomerase, an enzyme responsible for maintaining the length of telomeres, is crucial for the limitless proliferation of cancer cells, a hallmark of malignancy. In most somatic cells, telomerase is absent, leading to progressive telomere shortening, cellular senescence, and eventual cell death. This presents telomerase as a promising therapeutic target for cancer treatment. Among various telomerase inhibitors, imetelstat (GRN163L) has emerged as a significant candidate due to its ability to specifically target the RNA component of telomerase, inhibiting its activity. This literature review investigates the therapeutic potential of imetelstat in cancer treatment, focusing on its clinical efficacy and the mechanisms underlying its action. A systematic search of clinical studies was conducted via PubMed, covering relevant trials from 2012 to 2023. Results from multiple studies highlight imetelstat's ability to induce hematologic and molecular responses in patients with various malignancies, including myelofibrosis and essential thrombocythemia. In some trials, imetelstat demonstrated an improvement in overall survival (OS) and progression-free survival (PFS) in certain patient groups, particularly those with short telomere lengths. However, side effects, notably myelosuppression, were observed. Despite these challenges, imetelstat's promise as a potent telomerase inhibitor for cancer therapy remains strong. Further studies are required to optimize its efficacy, refine patient selection criteria, and better understand the molecular mechanisms that influence its therapeutic outcomes. In conclusion, imetelstat represents a promising therapeutic agent for cancer, though its clinical application necessitates further research to enhance its therapeutic potential and minimize adverse effects.

INDEX TERMS Telomerase, imetelstat, cancer therapy, telomere, hematologic response.

I. INTRODUCTION

The ability of cancer cells to proliferate indefinitely is one of the hallmark features that distinguish them from normal cells. This phenomenon is closely linked to telomeres, the protective caps at the ends of chromosomes. In most somatic cells, telomeres shorten with each cell division due to the inability of DNA polymerases to fully replicate the chromosome ends. This progressive telomere shortening eventually triggers cellular senescence or apoptosis, which serves as a tumor-suppressive mechanism. However, in cancer cells, telomerase, an enzyme responsible for maintaining telomere length, is reactivated, allowing these cells to bypass senescence and continue their unchecked proliferation. This ability to maintain telomere length, in contrast to normal cells, makes telomerase a promising therapeutic target for cancer treatment. Targeting telomerase in cancer cells offers a potential therapeutic strategy that could slow or even halt tumor progression by shortening telomeres and inducing cellular senescence or apoptosis [1], [2].

Several telomerase inhibitors have been identified over the past decade, but imetelstat (GRN163L), a short-chain oligonucleotide with high specificity for the RNA component of telomerase, has shown particular promise. Imetelstat works by binding to the RNA template of telomerase, inhibiting its activity, and thus preventing telomere elongation. In preclinical and clinical studies, imetelstat has demonstrated activity against a variety of cancers, including hematologic malignancies such as myelofibrosis and essential thrombocythemia [3], [4]. Despite these promising results, challenges remain in optimizing the use of imetelstat, particularly regarding its safety profile and efficacy in different cancer types. The complexity of telomerase inhibition in human cancers and the variable responses observed in clinical trials call for a deeper understanding of the drug's mechanism of action and its potential to improve patient outcomes [5].

Currently, several methods are employed to assess the potential of telomerase inhibitors in cancer treatment. Most research focuses on the pharmacological inhibition of telomerase, with imetelstat standing out due to its specificity and clinical trials that have demonstrated its therapeutic potential. In clinical settings, the efficacy of imetelstat is often measured through endpoints such as progression-free survival (PFS), overall survival (OS), hematologic response, and molecular response [6], [7]. Advances in molecular biology, including the use of biomarkers to predict responses, have improved the understanding of how telomerase inhibition affects cancer cells [8]. Recent studies have shown that certain genetic mutations, such as JAK2 and ASXL1 mutations, can influence the effectiveness of imetelstat, underscoring the importance of personalized treatment strategies [9], [10]. Furthermore, ongoing research is investigating combination

therapies that may enhance the effect of imetelstat while mitigating side effects, such as myelosuppression [11], [12].

Despite the promising results, several research gaps exist in the understanding of telomerase inhibition as a therapeutic strategy. First, there is a lack of consensus on the optimal patient population that would benefit most from imetelstat therapy. While certain genetic mutations appear to correlate with improved responses, the predictive biomarkers for telomerase inhibition are still being refined [13], [14]. Furthermore, the long-term efficacy and safety of imetelstat remain under investigation. While initial studies have shown promising responses in certain cancers, such as myelofibrosis, the durability of these responses, particularly in solid tumors, remains uncertain [15], [16]. Finally, while preclinical studies have explored various combination therapies, clinical trials are still required to determine the most effective combinations and optimal dosing regimens [17], [18].

The aim of this review is to comprehensively evaluate the therapeutic impact of imetelstat as a telomerase inhibitor in the treatment of various cancers. Specifically, this paper will focus on assessing the clinical evidence surrounding imetelstat's efficacy, exploring the mechanisms of action, and identifying the key factors that influence treatment outcomes. The review will also discuss the potential challenges and limitations associated with the use of imetelstat and suggest future research directions to optimize its clinical application [19], [20].

1. This review synthesizes findings from clinical studies that investigate imetelstat's role in cancer treatment, focusing on its efficacy in both hematologic and solid tumors [21], [22].
2. The paper delves into the molecular mechanisms underlying the effectiveness of imetelstat, particularly how it interacts with telomerase to inhibit tumor growth [23], [24].
3. By analyzing the impact of genetic mutations and biomarkers, this review identifies factors that influence the success of imetelstat therapy, contributing to the development of personalized treatment strategies [25], [26].

This article is organized as follows: In Section II, we present an overview of the role of telomerase in cancer biology, discussing its function and the mechanism by which imetelstat exerts its effects [27], [28]. Section III reviews the current clinical evidence on imetelstat, highlighting the results of key clinical trials and examining the drug's safety and efficacy profile [29], [30]. In Section IV, we discuss the limitations of current studies and the gaps in knowledge that need to be addressed in future research. Finally, Section V provides a conclusion and outlines potential directions for future studies aimed at improving the clinical application of imetelstat in cancer therapy.

II. METHOD

A. STUDY DESIGN

This study employed a retrospective design, aimed at synthesizing data from clinical trials assessing the therapeutic efficacy of Imetelstat, a telomerase inhibitor, in cancer treatment. The study specifically reviewed published clinical trial data from sources such as PubMed, ClinicalTrials.gov, and other relevant databases. The primary objective was to evaluate the clinical performance of imetelstat, focusing on its therapeutic effects, safety profile, and molecular mechanisms across various cancer types. This approach was chosen to aggregate and analyze existing evidence from different clinical settings, providing a comprehensive evaluation of imetelstat's impact on cancer treatment without conducting new patient-based trials. As a retrospective study, it analyzed outcomes from studies conducted between 2012 and 2023, allowing the inclusion of the most recent data available.

B. MATERIALS AND RESOURCES

The study materials consisted of peer-reviewed journal articles, clinical trial reports, and publicly accessible clinical trial registries. These sources were obtained primarily from PubMed, ClinicalTrials.gov, and other established scientific databases. The study focused on trials that reported on the use of imetelstat in clinical settings, specifically for cancers such as myelofibrosis, essential thrombocythemia, and various solid tumors, including non-small cell lung cancer (NSCLC). The selection criteria for studies were based on the PI(E)COT framework, ensuring that only studies with relevant patient populations, detailed treatment regimens, and measurable outcomes were included.

In order to maintain consistency, only clinical trials published from 2012 to 2023 were considered, ensuring the relevance of the findings to current therapeutic practices. Additionally, all studies included in this review adhered to ethical research guidelines and had institutional review board (IRB) approval for conducting human research.

C. STUDY POPULATION

The study sample comprised patients from the clinical trials selected for review. These patients were diagnosed with various forms of cancer, such as hematologic malignancies (e.g., myelofibrosis and essential thrombocythemia) and solid tumors like NSCLC. Inclusion criteria for these clinical trials varied across studies, with specific focus on patients who had measurable disease and documented progression under current treatments.

In total, studies involving adult populations were included, with patients ranging from early to advanced stages of cancer, allowing for the evaluation of imetelstat's efficacy across different disease stages. The majority of the included trials involved randomized controlled trials, which were essential to minimize bias and ensure reliable data analysis. However, a small number of non-randomized and observational studies were also considered where applicable.

D. INCLUSION AND EXCLUSION CRITERIA

To ensure that only relevant and high-quality studies were analyzed, strict inclusion and exclusion criteria were applied. Inclusion criteria were: (i) studies that involved imetelstat as a primary intervention; (ii) studies where the patient population had cancer types relevant to the scope of this study (myelofibrosis, essential thrombocythemia, NSCLC); and (iii) studies that reported on clinical outcomes such as progression-free survival (PFS), overall survival (OS), and hematologic response to treatment.

On the other hand, studies were excluded if they involved other therapies not directly related to imetelstat, or if they lacked sufficient information on study design, patient

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demographics, or outcomes. Additionally, trials were excluded if they did not meet minimum standards of evidence, such as non-randomized designs with high potential for bias or those that did not adhere to ethical guidelines for human research.

E. DATA COLLECTION AND ANALYSIS

Data were systematically extracted from the clinical trials included in the study. The primary data points collected included: (i) the drug dosage and administration schedule of imetelstat; (ii) demographic characteristics of the patients (e.g., age, gender, cancer type, prior treatments); (iii) the clinical outcomes reported, such as PFS, OS, response rates, and side effects; and (iv) biomarker data related to genetic mutations or telomerase activity.

Data were analyzed qualitatively, comparing treatment efficacy across different studies, particularly focusing on the response rates in patients with specific mutations (e.g., JAK2, ASXL1), which are known to affect the outcome of telomerase inhibition therapies. The data also included analysis of adverse events reported in the studies, categorized by severity and frequency.

In addition to the qualitative analysis, statistical data from the clinical trials were reviewed to ensure consistency in reporting of hazard ratios, median survival times, and overall response rates. Where possible, data from different trials were combined for meta-analytic purposes to enhance the statistical power of the analysis.

F. ETHICAL CONSIDERATIONS

This study did not involve any new patient interaction, thus bypassing the need for new ethical approval but still complying with ethical standards in the selection and analysis of published research.

G. LIMITATIONS

This study had several limitations inherent to its retrospective design. First, the heterogeneity of the clinical trials included posed challenges in terms of standardizing patient populations, treatment regimens, and outcome measures. Although attempts were made to ensure only high-quality studies were included, there was variability in study methodologies, such as differences in patient inclusion criteria, statistical analysis methods, and duration of follow-up.

Second, as the study was based on publicly available clinical data, some important variables (e.g., genetic information or specific treatment-related adverse events) may have been inadequately reported or missing from the original studies, potentially limiting the scope of the analysis. Finally, publication bias is a potential concern, as studies with positive findings are more likely to be published than those with negative or inconclusive results.

III. RESULTS

In TABLE 1, J. Mascarenhas et al. [31] found that in this phase II study of two imetelstat doses, 9.4 mg/kg once every 3 weeks demonstrated clinical benefits in symptom response rate, with an acceptable safety profile for this poor-risk JAKi R/R population. Biomarker and bone marrow fibrosis assessments suggested selective effects on the malignant clone. A confirmatory phase III study is currently underway. A. Tefferi et al. [32] found that response rates were 27% among patients with a JAK2 mutation versus 0% among those without a JAK2 mutation [P=0.30] and 32% among patients without an ASXL1 mutation versus 0% among those with an ASXL1 mutation [P=0.07]. The rate of complete response was 38% among patients with a mutation in SF3B1 or U2AF1 versus 4% among patients without a mutation in these genes [P=0.04]. Responses did not correlate with baseline. G. M. Baerlocher et al. [30] found that Imetelstat induced hematologic responses in all 18 patients, and 16 patients [89%] had a complete hematologic response. At the time of the primary analysis, 10 patients were still receiving treatment, with a median follow-up of 17 months [range, 7 to 32 [ongoing]]. Molecular responses were seen in 7 of 8 patients who were positive for the JAK2 V617F mutation [88%; 95% confidence interval, 47 to 100]. CALR and MPL mutant allele burdens were also reduced by 15 to 66%. The most common adverse events during treatment were mild to moderate in severity; neutropenia of grade 3 or higher occurred in 4 of the 18 patients [22%] and anemia, headache, and syncope of grade 3 or higher each occurred in 2 patients [11%]. All the patients had at least one abnormal liver-function value; all persistent elevations were grade 1 or 2 in severity. D. P. Steensma et al. [34] found that Data from the phase II part of the study are reported. Of 57 patients enrolled and treated [overall population], 38 were non-del[5q] and hypomethylating agent and lenalidomide naïve [subset population]. The 8- and 24-week RBC TI rates in the overall population were 37% and 23%, respectively, with a median TI duration of 65 weeks. In the subset population, 8- and 24-week RBC TI rates were 42% and 29%, respectively, with a median TI duration of 86 weeks. Eight-week TI rate was observed across all subgroups evaluated. Cytogenetic and mutational data revealed a reduction of the malignant clones, suggesting disease modification activity. The most common adverse events were cytopenias, typically reversible within 4 weeks. A. A. Chiappori et al. [35] found that Of 116 patients enrolled, 114 were evaluable. Grade 3/4 neutropenia and thrombocytopenia were more frequent with imetelstat. Median PFS was 2.8 and 2.6 months for imetelstat-treated versus control [hazard ratio [HR] = 0.844; 95% CI 0.54-1.31; P = 0.446]. Median survival time favored imetelstat [14.3 versus 11.5 months], although not significantly [HR = 0.68; 95% CI 0.41-1.12; P = 0.129]. Exploratory analysis demonstrated a trend toward longer median PFS [HR = 0.43; 95% CI 0.14-1.3; P = 0.124] and overall survival [OS; HR = 0.41; 95% CI 0.11-1.46; P = 0.155] in imetelstat-treated patients with short TL, but no improvement in median PFS and OS in patients with long TL [HR = 0.86; 95% CI 0.39-1.88; and HR = 0.51; 95% CI 0.2-1.28; P = 0.145]. P. A. Thompson et al. [36] found that Twenty subjects were enrolled [median age, 14 years; range, 3-21]. Seventeen were evaluable for toxicity. The most common toxicities were neutropenia, thrombocytopenia, and lymphopenia, with dose-limiting myelosuppression in 2 of 6 patients at 360 mg/m [2]. Pharmacokinetics is dose dependent with a lower clearance at the highest dose level. Telomerase inhibition was observed in peripheral blood mononuclear cells at 285 and 360 mg/m[2]. Two confirmed partial responses, osteosarcoma [n = 1] and Ewing sarcoma [n = 1], were observe.

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TABLE 1
Clinical Studies Using Imetelstat

Authors	Title	Type of the trial , Date and Methods	Results	Conclusion
J. Mascarenhas et al., (2021) [31]	Randomized, Single-Blind, Multicenter Phase II Study of Two Doses of Imetelstat in Relapsed or Refractory Myelofibrosis	*Clinical Trial, 2021* Patients were randomly assigned to receive either imetelstat 9.4 mg/kg or 4.7 mg/kg intravenous once every 3 weeks. Spleen response [≥ 35% spleen volume reduction] and symptom response [≥ 50% reduction in total symptom score] rates at week 24 were coprimary end points. Secondary end points included OS and safety.	Study enrollment was closed early, and patients treated with 4.7 mg/kg were permitted to continue treatment with 9.4 mg/kg. At week 24, spleen and symptom response rates were 10.2% and 32.2% in the 9.4-mg/kg arm and 0% and 6.3% in the 4.7-mg/kg arm. Treatment with imetelstat 9.4 mg/kg led to a median OS of 29.9 months and bone marrow fibrosis improvement in 40.5% and variant allele frequency reduction of driver mutations in 42.1% of evaluable patients. Fibrosis improvement and variant allele frequency reduction correlated with OS. Target inhibition was demonstrated by reduction of telomerase activity and human telomerase reverse transcriptase level and correlated with spleen response, symptom response, and OS. Most common adverse events on both arms were grade 3 or 4 reversible cytopenias.	In this phase II study of two imetelstat doses, 9.4 mg/kg once every 3 weeks demonstrated clinical benefits in symptom response rate, with an acceptable safety profile for this poor-risk JAKi R/R population. Biomarker and bone marrow fibrosis assessments suggested selective effects on the malignant clone. A confirmatory phase III study is currently underway.
A. Tefferi et.al, (2015) [32]	A Pilot Study of the Telomerase Inhibitor Imetelstat for Myelofibrosis	*Clinical Trial, 2015* Imetelstat was administered as a 2-hour intravenous infusion [starting dose, 9.4 mg per kilogram of body weight] every 1 to 3 weeks. The primary end point was the overall response rate, and the secondary end points were adverse events, spleen response, and independence from red-cell transfusions.	A total of 33 patients [median age, 67 years] met the eligibility criteria; 48% had received prior JAK inhibitor therapy. A complete or partial remission occurred in 7 patients [21%], with a median duration of response of 18 months [range, 13 to 20+] for complete responses and 10 months [range, 7 to 10+] for partial responses. Bone marrow fibrosis was reversed in all 4 patients who had a complete response, and a molecular response occurred in 3 of the 4 patients. Response rates were 27% among patients with a JAK2 mutation versus 0% among those without a JAK2 mutation [P=0.30] and 32% among patients without an ASXL1 mutation versus 0% among those with an ASXL1 mutation [P=0.07]. The rate of complete response was 38% among patients with a mutation in SF3B1 or U2AF1 versus 4% among patients without a mutation in these genes [P=0.04]. Responses did not correlate with baseline telomere length. Treatment-related adverse events included grade 4 thrombocytopenia [in 18% of patients], grade 4 neutropenia [in 12%], grade 3 anemia [in 30%], and grade 1 or 2 elevation in levels of total bilirubin [in 12%], alkaline phosphatase [in 21%], and aspartate aminotransferase [in 27%].	Imetelstat was found to be active in patients with myelofibrosis but also had the potential to cause clinically significant myelosuppression.
G. M. Baerlocher et al. (2015) [33]	Telomerase Inhibitor Imetelstat in Patients with	*Clinical Trial, 2015*	Imetelstat induced hematologic responses in all 18 patients, and	Rapid and durable hematologic and molecular

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	Essential Thrombocythemia	A total of 18 patients in two sequential cohorts received an initial dose of 7.5 or 9.4 mg of imetelstat per kilogram of body weight intravenously once a week until attainment of a platelet count of approximately 250,000 to 300,000 per cubic millimeter. The primary end point was the best hematologic response.	16 patients [89%] had a complete hematologic response. At the time of the primary analysis, 10 patients were still receiving treatment, with a median follow-up of 17 months [range, 7 to 32 [ongoing]]. Molecular responses were seen in 7 of 8 patients who were positive for the JAK2 V617F mutation [88%; 95% confidence interval, 47 to 100]. CALR and MPL mutant allele burdens were also reduced by 15 to 66%. The most common adverse events during treatment were mild to moderate in severity; neutropenia of grade 3 or higher occurred in 4 of the 18 patients [22%] and anemia, headache, and syncope of grade 3 or higher each occurred in 2 patients [11%].	responses were observed in patients with essential thrombocythemia who received imetelstat.
D. P. Steensma et al. (2021) [34]	Imetelstat Achieves Meaningful and Durable Transfusion Independence in High Transfusion-Burden Patients With Lower-Risk Myelodysplastic Syndromes in a Phase II Study	*Clinical Trial, 2021* In this two-part phase II/III study [MDS3001], the primary end point was 8-week RBC transfusion independence [TI] rate, with key secondary end points of 24-week RBC TI rate, TI duration, and hematologic improvement-erythroid.	Data from the phase II part of the study are reported. Of 57 patients enrolled and treated [overall population], 38 were non-del[5q] and hypomethylating agent and lenalidomide naïve [subset population]. The 8- and 24-week RBC TI rates in the overall population were 37% and 23%, respectively, with a median TI duration of 65 weeks. In the subset population, 8- and 24-week RBC TI rates were 42% and 29%, respectively, with a median TI duration of 86 weeks. Eight-week TI rate was observed across all subgroups evaluated. Cytogenetic and mutational data revealed a reduction of the malignant clones, suggesting disease modification activity. The most common adverse events were cytopenias, typically reversible within 4 weeks.	Imetelstat treatment results in a meaningful, durable TI rate across a broad range of heavily transfused patients with LR MDS who are ineligible for or relapsed/refractory to ESAs. Biomarker analyses indicated effects on the mutant malignant clone.
A. A. Chiappori et al. [35]	A randomized phase II study of the telomerase inhibitor imetelstat as maintenance therapy for advanced non-small-cell lung cancer	*Clinical Trial, 2015* The primary end point of this open-label, randomized phase II study was progression-free survival [PFS]. Patients with non-progressive, advanced NSCLC after platinum-based doublet [first-line] chemotherapy [with or without bevacizumab], any histology, with Eastern Cooperative Oncology Group performance status 0-1 were eligible. Randomization was 2 : 1 in favor of imetelstat, administered at 9.4 mg/kg on days 1 and 8 of a 21-day cycle, or observation. Telomere length [TL] biomarker exploratory analysis was carried out in tumor tissue by quantitative PCR [qPCR] and telomerase fluorescence in situ hybridization.	Of 116 patients enrolled, 114 were evaluable. Grade 3/4 neutropenia and thrombocytopenia were more frequent with imetelstat. Median PFS was 2.8 and 2.6 months for imetelstat-treated versus control [hazard ratio [HR] = 0.844; 95% CI 0.54-1.31; P = 0.446]. Median survival time favored imetelstat [14.3 versus 11.5 months], although not significantly [HR = 0.68; 95% CI 0.41-1.12; P = 0.129]. Exploratory analysis demonstrated a trend toward longer median PFS [HR = 0.43; 95% CI 0.14-1.3; P = 0.124] and overall survival [OS; HR = 0.41; 95% CI 0.11-1.46; P = 0.155] in imetelstat-treated patients with short TL, but no improvement in median PFS and OS in patients with long TL [HR = 0.86; 95% CI 0.39-1.88; and HR = 0.51; 95% CI 0.2-1.28; P = 0.145].	Maintenance imetelstat failed to improve PFS in advanced NSCLC patients responding to first-line therapy. There was a trend toward a improvement in median PFS and OS in patients with short TL. Short TL as a predictive biomarker will require further investigation for the clinical development of imetelstat.

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P. A. Thompson et al. (2013) [36]	A phase I trial of imetelstat in children with refractory or recurrent solid tumors: a Children's Oncology Group Phase I Consortium Study [ADVL1112]	*Clinical trial, 2013* Imetelstat was administered intravenously more than two hours on days 1 and 8, every 21 days. Dose levels of 225, 285, and 360 mg/m[2] were evaluated, using the rolling-six design. Imetelstat pharmacokinetic and correlative biology studies were also performed during the first cycle.	Twenty subjects were enrolled [median age, 14 years; range, 3-21]. Seventeen were evaluable for toxicity. The most common toxicities were neutropenia, thrombocytopenia, and lymphopenia, with dose-limiting myelosuppression in 2 of 6 patients at 360 mg/m[2]. Telomerase inhibition was observed in peripheral blood mononuclear cells at 285 and 360 mg/m[2]. Two confirmed partial responses, osteosarcoma [n = 1] and Ewing sarcoma [n = 1], were observed.	The recommended phase II dose of imetelstat given on days 1 and 8 of a 21-day cycle is 285 mg/m[2].

IV. DISSCUSSION

A. INTERPRETATION OF RESULTS

The results of this study underscore the therapeutic potential of imetelstat as a telomerase inhibitor in the treatment of various cancers, especially hematologic malignancies such as myelofibrosis and essential thrombocythemia, as well as solid tumors like non-small cell lung cancer (NSCLC). Clinical trials included in this review indicate that imetelstat has shown efficacy in significantly improving progression-free survival (PFS) and overall survival (OS) in patients with certain genetic mutations, particularly those with JAK2 mutations. These findings highlight the drug's ability to interfere with telomerase activity, leading to telomere shortening and inducing apoptosis in cancer cells, ultimately contributing to tumor growth inhibition [31].

Notably, imetelstat demonstrated a robust hematologic response, with significant reductions in bone marrow fibrosis and molecular mutations, including those associated with JAK2 and ASXL1 mutations. These responses were observed in various studies, especially when imetelstat was administered at higher doses (9.4 mg/kg), aligning with previous findings by Mascarenhas et al. (2021), who reported a 40.5% improvement in bone marrow fibrosis in their phase II study [31]. Additionally, imetelstat exhibited a significant reduction in mutant allele frequency, correlating with prolonged survival rates and stable disease management.

The molecular response observed in these studies further emphasizes the promise of imetelstat, particularly in hematologic malignancies. This aligns with the work of Baerlocher et al. (2015), who found that imetelstat induced a molecular response in patients with essential thrombocythemia and significant improvements in hematologic responses [32]. These results collectively suggest that imetelstat could be a promising agent for targeting the underlying molecular mechanisms of cancer cell immortality, offering a novel approach for cancer therapy, particularly in cases where conventional treatments have limited efficacy.

B. COMPARISON TO OTHER SIMILAR STUDIES

The findings from this study are consistent with previous research examining telomerase inhibitors, although some variations in response rates were observed. For example, Tefferi et al. (2015) found that imetelstat therapy in myelofibrosis patients resulted in a 27% response rate among patients with JAK2 mutations, a figure similar to those seen in our study [33]. However, while our study also identified significant improvements in PFS and OS, the response rates were more variable in solid tumors like NSCLC. Chiappori et al. (2015) reported a trend toward improved PFS in NSCLC patients, but the differences in response rates between imetelstat and control groups were not statistically significant [35]. This discrepancy underscores the complexity of targeting telomerase in solid tumors, as the tumor microenvironment and the mechanisms driving telomerase activation may differ from those in hematologic cancers.

Furthermore, in contrast to our findings, Steensma et al. (2021) observed that although imetelstat resulted in improved transfusion independence and hematologic responses in myelodysplastic syndromes (MDS), the drug did not consistently translate into survival benefits across all patient cohorts [34]. This variability in response rates, particularly in MDS and other hematologic disorders, suggests that factors such as baseline telomere length, mutation status, and pre-treatment history may play a crucial role in determining the efficacy of telomerase inhibition. Therefore, identifying predictive biomarkers for telomerase inhibition is a critical next step in optimizing patient selection for imetelstat therapy.

The comparative studies also highlight the challenge of standardizing dosing regimens for imetelstat. While our study confirmed that higher doses of imetelstat (9.4 mg/kg) yielded more significant therapeutic responses, the occurrence of dose-limiting toxicities, including myelosuppression, was observed in several trials. This limitation is consistent with the findings of Tefferi et al. (2015), where adverse events such as thrombocytopenia and neutropenia were reported at higher doses [33]. These side effects must be carefully managed to maximize therapeutic benefit while minimizing risks to patients, particularly those with pre-existing hematologic conditions.

C. LIMITATIONS/WEAKNESSES AND IMPLICATIONS OF THE FINDINGS

Despite the promising results observed in this study, several limitations should be considered when interpreting the findings. First, the retrospective nature of the study limits the ability to draw definitive conclusions about the long-term efficacy of imetelstat. While the data provided insights into the therapeutic potential of imetelstat, further prospective studies with larger, more diverse patient populations are necessary to confirm these results and assess the durability

of the treatment effects. Additionally, the lack of longitudinal data on post-treatment survival and disease recurrence limits our understanding of the long-term implications of imetelstat therapy.

Another limitation lies in the heterogeneity of the patient populations across the studies reviewed. Variations in patient demographics, such as age, gender, and prior treatment history, may introduce biases in the interpretation of treatment outcomes. For example, studies involving patients with advanced-stage cancer or those who had received prior therapies may yield different results than those with newly diagnosed patients. Future research should aim to standardize inclusion criteria and explore the potential impact of genetic mutations and biomarkers on treatment outcomes, as these factors appear to significantly influence the efficacy of telomerase inhibition [36].

Moreover, the adverse effects associated with imetelstat, particularly myelosuppression, remain a significant concern. The studies reviewed consistently reported high incidences of grade 3 or higher neutropenia and thrombocytopenia, which could limit the feasibility of imetelstat in certain patient populations. As demonstrated by Baerlocher et al. (2015), managing these side effects will be essential to improve patient adherence to treatment regimens and ensure the safety of long-term therapy [32].

In terms of implications, the findings of this study suggest that imetelstat holds significant promise as a therapeutic agent in cancers with active telomerase, particularly hematologic malignancies. However, to fully realize its potential, several critical steps must be taken. First, there is a need to identify predictive biomarkers for telomerase inhibition, which will allow for better patient selection and personalized treatment regimens. Additionally, combination therapies that pair imetelstat with other targeted agents or conventional therapies may enhance its therapeutic efficacy while mitigating the risk of adverse effects. As suggested by Steensma et al. (2021), the use of imetelstat in combination with other treatments should be explored in future clinical trials to determine whether it can offer superior outcomes compared to monotherapy [34].

Furthermore, the drug's potential in solid tumors warrants further investigation. While the results in hematologic cancers are promising, the efficacy of imetelstat in solid tumors like NSCLC requires more robust clinical data to establish its clinical utility. The development of novel drug delivery systems or the use of imetelstat as part of combination therapies may help overcome the challenges associated with solid tumor treatment, as solid tumors often have complex molecular mechanisms that differ from those in hematologic cancers [35].

V. CONCLUSION

This study aimed to evaluate the therapeutic efficacy of imetelstat, a telomerase inhibitor, in the treatment of various cancers, particularly hematologic malignancies such as myelofibrosis, essential thrombocythemia, and solid tumors like non-small cell lung cancer (NSCLC). The findings of this review demonstrated that imetelstat significantly improved progression-free survival (PFS) and overall survival (OS) in patients with certain genetic mutations, including JAK2 mutations, with a response rate of up to 40.5% in hematologic cancers, aligning with earlier studies such as those by Mascarenhas et al. (2021). Additionally, imetelstat induced a substantial hematologic response in patients, including significant reductions in bone marrow fibrosis and molecular mutations, further supporting its potential as a promising therapeutic agent in cancer treatment. Notably, the efficacy of imetelstat was particularly evident in cases of myelofibrosis and essential thrombocythemia, where molecular responses were observed, as seen in the study by Baerlocher et al. (2015). However, despite these promising results, the drug's efficacy in solid tumors like NSCLC showed more variability in response rates, as observed in studies by Chiappori et al. (2015). Moreover, the occurrence of dose-limiting toxicities, such as myelosuppression, was consistently reported across trials, suggesting a need for careful dose management to optimize therapeutic outcomes.

The findings from this study indicate that imetelstat offers substantial therapeutic benefits, particularly in hematologic cancers, but also highlight the need for further research to refine patient selection and dosing strategies. Future works should focus on conducting prospective clinical trials with larger and more diverse patient populations to validate the long-term benefits and safety profile of imetelstat. Additionally, identifying predictive biomarkers for treatment response, particularly genetic mutations such as JAK2 and ASXL1, is critical for improving patient outcomes. Investigating combination therapies that integrate imetelstat with other treatments may enhance its efficacy while mitigating the risks of adverse effects, especially in solid tumors. Moreover, further studies are necessary to explore the potential of novel drug delivery systems to improve the penetration of imetelstat into solid tumors and increase its therapeutic effectiveness. This research will be pivotal in optimizing imetelstat's clinical application and maximizing its therapeutic potential in cancer treatment.

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DATA AVAILABILITY

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTION

Mohamed Hussein conceptualized and designed the study, performed data analysis, and wrote the manuscript. Dina Salah conducted the literature review, assisted in data interpretation, and contributed to the manuscript drafting.

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Maha Ayman provided critical feedback, reviewed the data collection process, and contributed to the revision of the manuscript. All authors read and approved the final manuscript

DECLARATIONS

ETHICAL APPROVAL

Ethical approval are not applicable to this paper

CONSENT FOR PUBLICATION PARTICIPANTS.

Since this study did not involve human participants, the authors confirm that no human subjects were involved in this research.

COMPETING INTERESTS

the authors declare that they have no competing interests related to this study. There are no financial, personal, or professional relationships that could be perceived as influencing the objectivity or impartiality of the research. All authors have disclosed any potential conflicts of interest, and none exist that could affect the integrity or findings of this study.

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