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Therapeutic impact of Telomerase Inhibitor Imetelstat: A Literature Review

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ABSTRACT The immortal phenotype of cancer cells is a significant trait, and in the vast majority of malignancies, the enzyme telomerase is essential for sustaining the cancer cells' limitless capacity for replication. The absence of telomerase expression and the lack of an immortal phenotype in normal adult tissues suggest that telomerase is a prospective therapeutic target for the treatment of a variety of tumor forms. At every cell division, telomeres will shrink if telomerase is not active. Apoptosis, cell senescence, and chromosomal instability are initiated when the telomeres become critically short. Telomeres are stabilized in the majority of rapidly expanding cancers by reactivating telomerase. In numerous tumor forms, it has been demonstrated that telomerase inhibition inhibits the development of cancer cells. Telomerase inhibitors have been discovered over the past 10 years as a result of substantial basic research into the mechanisms regulating telomeres, which may offer a potent, nearly universal cancer treatment approach. A short-chain oligonucleotide called imetelstat [GRN163L, Geron Corporation] has a high affinity and specificity for the RNA component of telomerase's template region [hTR or hTERC]. Researchers conduct an examination of articles that are in accordance with the issue to be studied. Articles used in literature review are obtained through the database of international journal providers through PubMed, we investigated clinical studies and discussed what happened in these clinical studies and the extent of the effectiveness of imetelstat in treatment of cancer. Articles proved that imetelstat could enhance cancer treatment. Articles proved that Imetelstat is promising therapeutic agents for cancer treatment. In this review, we suggest that formulating and following treatment, Further studies are needed to determine the related mechanisms to enhance Imetelstat efficacy.

INDEX TERMS Cancer, Immortal, Telomerase, Telomere, Imetelstat.

I. INTRODUCTION

The 5–15 kb double-stranded (ds) telomeric repeats 5′-TTAGGG-3′ that make up the chromosome ends, or telomeres, result in a single-stranded (ss) 3′ G-overhang. For telomeric stability, the G-quadruplex structure that G-overhangs can create is essential. The significance of telomeres to maintaining chromosomal integrity and cellular function is demonstrated by the evolutionary preservation of their repeating sequences. However, each cell division results in a steady loss of telomeric repeats because DNA polymerase is unable to replicate the chromosome's end during lagging strand synthesis. Eventually, the telomeres become critically short, which causes cell senescence. Progressive telomere shortening can result in chromosome fusions, genomic instability, and ultimately loss of cell viability and tumor development if cells do not experience senescence. The enzyme telomerase, which is expressed in specific cell types, solves the problem of end replication [1,2]

Reverse transcriptase called telomerase is in charge of telomere replication. To start extending the telomeric sequence, telomerase binds to the 3′ G-overhang, which serves as its substrate. The 3′-end is moved when the first repetition is added, allowing telomerase to add more repeats. Human [h]telomerase RNA [TR] and human [h]telomerase reverse transcriptase are the two components that make up telomerase (TERT). The RNA template for telomeric amplification and specific structures for enzymatic stability are both found in the TR component. The telomerase N-terminal domain, the TR-binding domain, the reverse transcriptase domain, and the C-terminal extension are the four functional domains that make up the catalytic TERT subunit [3].

The primary purpose of Telomeres is to shield the ends of chromosomes against deterioration and the loss of genetic material. Telomeres shorten and lose any genetic material that is necessary for the cell during cell division [4,5,6,7]. DNA processing at the ends of chromosomes and the end replication phenomena were combined to create the process. After the RNA primer is removed during semiconservative replication, the delayed strand [produced by the fusion of Okazaki fragments] has an imperfect 5′ end. Because the DNA polymerases involved in the replication process only create the polynucleotide chain in the 5′ to 3′ orientation, the ensuing gap cannot be filled. Telomeres shield chromosomes against exonuclease attack, aberrant recombination, chromosome fusion [which prevents chromosomal aberrations such translocations, duplications, and deletions], and degradation [8,9,10,11].

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Although telomere lengthening is a capability acquired by tumors with telomerase activation, it has been noted that prostate cancers have shorter telomeres than normal tissues. Barthel et al. recently used whole genome sequencing or whole exome sequencing data from The Cancer Genome Atlas (TCGA) to analyze the telomere length of 18,430 samples from 31 different cancer cohorts. When compared to normal samples, they showed that 70% of cohorts had shorter telomeres, while the remaining 30% were either known to be or assumed to be regulated by ALT. Fluorescence in situ hybridization staining of both nevus and melanoma sections further supports this finding [12,13,14,15].

Given that telomere lengthening caused by telomerase is crucial for the endless proliferation of TERT-positive cancer cells, genetic or pharmacological reduction of telomerase activity in cancer cells results in gradual telomere shortening and eventual cell senescence or apoptosis [16,17,18]. Theoretically, cancer cells with shorter telomeres would exhibit the anticancer effect of telomerase suppression sooner. In actuality, a biomarker for telomerase inhibitors that is predictive of short telomere length exists [19,20]

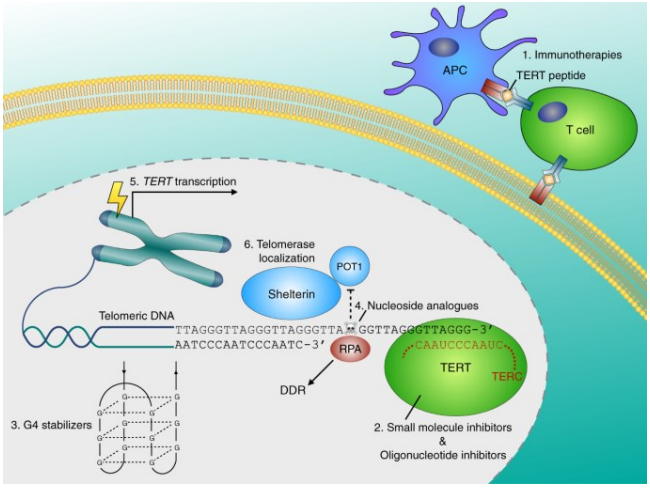

FIGURE 1. Targeting telomerase for cancer therapy [21]

A study on haematopoietic malignancies provided the first proof that a small population of stem cells sustains human malignancy. Premalignant, chronic, and acute stages of hematopoietic malignancies can be distinguished, with the last being the most progressed and cancerous. The progression of the disease into a more malignant and acute stage, such as acute lymphoid or myeloid leukemia, is known to occur in the premalignant stage, such as MDS, and the chronic stage, such as CML or chronic lymphoid leukemia. Telomere shortening in HSCs is thought to be a risk factor in this pathway that aids in the emergence of chromosomal instability and malignant transformation [22, 23]. Telomere shortening in DKC patients is associated with a higher chance of developing haematological neoplasia, supporting mutation [P=0.30] and 32% among patients without an ASXL1 mutation versus 0% among those with an ASXL1 this theory. Similar to haematopoietic malignancies, a number of solid tumors, particularly breast and brain tumours, are thought to be produced and/or spread by CSCs [24,25].

As it can be challenging to identify and isolate CSCs from most solid tumors, it is unclear how CSCs preserve their unique capacity for replication. CSCs should, however, have telomere-lengthening processes. No matter where CSCs, regular stem cells, committed progenitor cells, or differentiated cells come from [26]. In light of the fact that telomere shortening, and cellular senescence are inevitabilities in these initial cells, with the exception of some Mesenchymal Stem Cells [MSCs], CSCs may have acquired immortality through mutational events in telomere-lengthening mechanisms, typically the activation of telomerase. The stabilization of telomeres in premalignant lesions to stop the activation of telomerase and transformation to CSCs, the identification of specific marker proteins in CSCs in each organ, and the inhibition of telomerase in CSCs to limit proliferation capacity and induce apoptosis, according to theory, are likely to optimize screening and therapeutic interventions as novel anticancer strategies [26,27]. In this review we investigated clinical studies and discussed what happened in these clinical studies and the extent of the effectiveness of imetelstat in treatment of cancer.

II. METHODOLOGY

Researchers conduct an examination of articles that are in accordance with the issue to be studied. Determination of literature search keywords [search string based on PI [E] COT framework [P= patient/problem; I/E= exposure / implementation; C= control/comparison intervention, O=outcome, T=time] because a good question will help determine the scope of the review and help the strategy of finding the article. Articles used in literature review are obtained through the database of international journal providers through PubMed, from 2012-2023, Clinical Trials only. Author opens www.PubMed.com. 1.Inclusion Criteria Population or sample is Telomerase Inhibitor Imetelstat for Cancer. 2.Exclusion Criteria Population or sample other than Telomerase Inhibitor Imetelstat for Cancer.

III. RESULTS AND DISCUSSION

In TABLE 1, J. Mascarenhas et al. [28] 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. [29] found that response rates were 27% among patients with a JAK2 mutation versus 0% among those without a JAK2

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. [31] 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. [32] 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. [33] 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.

TABLE 1
Clinical studies using Imetelstat.

Authors	Title	Type of the trial , Date and Methods	Results	Conclusion
J. Mascarenhas et al., [28]	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.[29]	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. [30]	Telomerase Inhibitor Imetelstat in Patients with Essential Thrombocythemia	*Clinical Trial, 2015* 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.	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%].	Rapid and durable hematologic and molecular responses were observed in patients with essential thrombocythemia who received imetelstat.

D. P. Steensma et al. [31]	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. [32]	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.
P. A. Thompson et al. [33]	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. CONCLUSION

DNA sequences with the repeated pattern TTAGGG make up vertebrate telomeres. The telomerase complex is made up of a telomerase reverse transcriptase [TERT] catalytic subunit and a telomerase RNA component [TERC]. The rate-limiting component for telomerase activity, TERT, catalyzes the insertion of DNA tandem repeats using TERC as a template . Other elements, such as the sheltering proteins TERF1 and TERF2, are crucial in the regulation of telomerase. Genome instability is avoided by telomeres, which shield the ends of chromosomes from end-to-end fusion and exonucleolytic destruction. Significantly, telomeric DNA shortens with each cell division in the majority of human cells, resulting in the buildup of dangerously short telomeres and the absence of detectable telomerase activity in the majority of somatic tissues, which ultimately leads to replicative senescence. Cancer cells were demonstrated to be dependent on telomere maintenance mechanisms in order to gain the ability to proliferate indefinitely and to avoid the genetic havoc brought on by telomere malfunction, which is consistent with the role of telomere shortening in tumor suppression. In mammalian cells, two telomere maintenance mechanisms have been discovered. The telomerase enzyme, which can generate telomeres from scratch, is used by the majority of human malignancies. Nevertheless, alternative telomere lengthening mechanisms [ALT] are activated in 10%–20% of human malignancies, but the molecular processes governing ALT activation are still poorly understood. In mouse models, telomerase inhibition can slow tumor growth, but ALT activation is what causes tumor recurrence. Imetelstat is a small oligonucleotide, comprised of nucleic acid and a lipid moiety. Imetelstat, a telomerase inhibitor, works by inhibiting telomerase in cells with overactive telomerase and short telomere lengths, and it is essential for maintaining healthy hematopoiesis. After infusion, the medication binds to the RNA component of telomerase's template region, inhibiting the enzyme's activity. Imetelstat was found to be active in patients with myelofibrosis but also had the potential to cause clinically significant myelosuppression. Rapid and durable hematologic and molecular responses were observed in patients with essential thrombocythemia who received imetelstat. While in other studies responses did not correlate with baseline telomere length. Further studies are needed to determine the related mechanisms to enhance imetelstat efficacy in treatment.

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