Drugs of the Future 2012, 37(2): 111-118

CCC: 0377-8282/2012
DOI: 10.1358/dof.2012.37.2.1779019

MONOGRAPH

IMETELSTAT SODIUM

Rec INN; USAN

Telomerase-Targeting Oligonucleotide Inhibitor
Oncolytic

GRN-163L

5'-[*O*-[2-Hydroxy-3-[(1-oxohexadecyl)amino]propyl] hydrogen phosphorothioate]d(3'-amino-3'-deoxy-*P*-thio)(T-A-G-G-G-T-T-A-G-A-C-A-A) DNA sodium salt (1:13)
3'-Amino-3'-deoxy-*P*-thiothymidylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'–5')-3'-amino-3'-deoxy-*P*-thiothymidylyl-(3'–5')-3'-amino-3'-deoxy-*P*-thiothymidylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thiocytidylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'–5')-3'-amino-2',3'-dideoxy-*P*-thioadenosine 5'-[*O*-[2-hydroxy-3-(hexadecanoylamino)propyl] hydrogen phosphorothioate] tridecasodium salt
13-Mer thiophosphoramidate oligonucleotide whose sequence is 3'-AACAGATTGGGAT-5' and where the 5'-position is conjugated to palmitoylamidoglycerol through a thiophosphate group

CAS: 868169-64-6
EN: 367364

SUMMARY

A cell's life span is determined by the length of telomere caps on the ends of the chromosomes that prevent degradation and are maintained by telomerase. Telomerase is not expressed in somatic cells but is highly expressed in most cancer cells, where it acts to extend cell life span and promote tumor growth. Telomerase inhibitors specifically target telomerase activity in cancer cells to induce cell death and diminish tumor growth. Imetelstat sodium is an oligonucleotide-based telomerase inhibitor that binds to the single-stranded stretch of telomeric DNA that acts as a template recognition site for the human telomerase enzyme complex. In preclinical experiments, imetelstat has potently inhibited telomerase activity in vitro and in vivo, resulting in telomeric shortening concomitant with reduced proliferation, the induction of apoptosis, increased cell death, reduction in tumor establishment and growth, and increased animal survival. Imetelstat is currently in phase I/II trials for a number of cancer types.

Key words: Telomerase inhibitor – Cancer – Imetelstat sodium – GRN-163L

BACKGROUND

Imetelstat sodium (GRN-163L) is a lipid-based conjugate of the first-generation 13-mer oligonucleotide GRN-163 (1), which acts as a potent and specific telomerase inhibitor. Telomeres are composed of simple repetitive DNA sequences that are located at the terminal ends of chromosomes. They function to protect chromosomes from degradation or prevent fusion with neighboring chromosomes during cellular proliferation, both of which can lead to mutations and the development of cancer (2). With each successive cycle of cell replication, and therefore chromosome replication, the telomeres progressively shorten. Shortening disrupts the structural formation of the protective telomere cap at the end of the chromosome. Loss of this structure leads to chromosome instability and mimics DNA damage, causing the cell to initiate senescence and programmed cell death (3). In essence, the length of telomeres governs the lifespan of a cell.

Eukaryotic telomeres possess a 3′ overhang that prevents replication by DNA polymerase because of the lack of a 5′ priming site. Replication of chromosomal ends is instead carried out by telomerases. Telomerases are ribonucleoprotein complexes consisting of a telomerase reverse transcriptase (TERT), an RNA primer sequence (telomerase RNA component; TERC) and other associated proteins. Telomerases extend telomere length by the addition of the six nucleotides TTAGGG, thereby extending cellular lifespan beyond the Hayflick limit, which is defined as the number of divisions a cell will undergo dependent on telomere length (extensively reviewed in 3-6).

Telomerase is rarely or only transiently expressed in somatic cells. The shortening of telomeres can cause cell death, but may also cause a cell to become cancerous. This may appear to be contradictory to the unregulated proliferation seen in most tumors, as shortened telomeres would surely lead to cell death; however, it is well established that telomerase is highly expressed in more than 90% of cancer cell lines (7). The expression of telomerase in cancer cells is one of the factors supporting enhanced proliferation and malignant tumor growth as cells exceed their lifespan; the action of telomerases maintains, and in some cases increases, telomere length. More recent evidence suggests that telomerase may have additional functions in cancerous cells, and delineating these functions may present further targets for the development of telomerase inhibitors (8). It is hardly surprising that with such ubiquitous expression in distinct cancer cell types and such a major role in tumor progression, the development of telomerase inhibitors as a new class of drugs to treat cancer has become an attractive challenge.

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The first telomerase inhibitor produced was the small molecule BIBR-1532, which blocks the catalytic telomerase activity and demonstrated initial promise in preclinical experiments. However, despite the impressive efficacy of BIBR-1532 to inhibit telomerase activity, induce telomere shortening and inhibit cell growth in cancer cell lines (9), the drug exhibited poor bioavailability (10). As a proof of concept, BIBR-1532 paved the way for the continued research into telomerase inhibitors as broad-spectrum antitumor agents. Other approaches for telomerase inhibition have included the development of antisense oligonucleotides (11), enzyme inhibitors (12, 13), dominant-negative constructs (14-17) and ribozymes that act to cleave TERC from TERT (18, 19).

Geron developed imetelstat sodium (GRN-163L), the first potent and specific telomerase inhibitor with good tissue distribution and bioavailability. Imetelstat sodium has shown enhanced telomerase inhibitory properties, as well as vastly improved cellular uptake and biodistribution compared to earlier unmodified oligonucleotides (20, 21). Imetelstat sodium elicits inhibition of telomerase activity by high-affinity, specific, competitive binding to a template recognition sequence of TERC in the active site of TERT, thus preventing interaction with the 3′ overhang of the telomere (22-24). Recent studies have hinted at novel mechanisms of action that function independently of telomere shortening. In glioblastoma cell lines and cancer stem cells, imetelstat sodium decreased the number of colony-forming units and inhibited growth by interfering with casein kinase II signaling (6). Uncovering further novel mechanisms of action should lead to the development of drugs or the use of preexisting compounds that could work in combination with imetelstat sodium to bring about a synergistic therapeutic benefit. In 2005, imetelstat sodium progressed into phase I trials and is currently in phase II development in various types of cancer.

PRECLINICAL PHARMACOLOGY

Since telomerase is highly active in a large percentage of cancerous cells and in cancer stem cells, the efficacy of imetelstat sodium to induce telomerase inhibition has been extensively evaluated in numerous human cancer cell lines, including breast, lung, blood, prostate, pancreas, ovarian and liver cancer cells. Imetelstat sodium-mediated telomerase inhibition has also been assessed in multiple murine xenograft models.

In 13 solid tumor cell lines representing various cancer types, IC_{50} values ranged from 0.15 to 1.35 μM, demonstrating the high-affinity binding of imetelstat sodium to its target (21).

In the human breast cancer cell lines MDA-MB-231, MCF7, SK-BR-3, 21NT, HCC1937, HCC1937+wt*BRCA1*, and in tumorigenic human mammary epithelial (HME) HME-50T cells, imetelstat sodium (1-2.5 μM applied every 3-4 days) resulted in short-term toxicity-free telomerase inhibition in a concentration-dependent manner. Telomerase inhibition was still evident 72 hours following a single application of the drug. Inhibition of telomerase occurred concomitant with progressive telomere shortening and decreases in tumorigenicity. Interestingly, the potency of telomerase inhibition and the antitumorigenic properties varied for each cell line, although they all displayed similar initial telomere lengths. Pretreatment with imetelstat sodium resulted in a reduction in colony formation of 58%, 70%, 83.7% and 92%, respectively, in HME50-T, MCF7, HCC-1937 and MDA-MB-231 cells. Similar experiments performed using a mismatched oligonucleotide or in mammary epithelium or CFB8 endothelial progenitor cells, which harbor endogenous telomerase activity, demonstrated the specificity of imetelstat sodium action in targeting only cancerous cells (21, 22, 25).

Further assessment in human breast adenocarcinoma MDA-MB-231 and MDA-MB-435 cell lines supported similar telomerase inhibition potential for imetelstat sodium. Twice-weekly administration of the drug (1 μM) resulted in telomerase inhibition within 48 hours and up to 6 days, decreasing telomere length, formation potential and cell invasiveness. The ability of imetelstat sodium to inhibit proliferation varied between the cell lines, with MDA-MB-435 cells demonstrating a decrease in proliferation and senescence by week 6, while a decreased proliferation rate was only observed after 12 weeks of administration in MDA-MB-231 cells (24). Several other investigations have demonstrated the efficacy of imetelstat sodium in inhibiting telomerase activity, and inducing telomere shortening in MDA-MB-231 cells, with an impact on cell proliferation and viability observed within 14 days of commencement of exposure (26).

In other studies, imetelstat sodium (10 μM) elicited marked inhibition of telomerase in MCF7 and MDA-MB-231 cells (97% and 87%, respectively; $P \leq 0.0002$). Most cancer stem cells (CSCs), which are thought to maintain tumor progression, are generally refractory to many drugs. In CSCs derived from MCF7 clonal cells, long-term treatment of mammospheres with imetelstat sodium (10 μM over a 4-week period) reduced cell proliferation, resulting in cell death within 3 weeks and the absence of viable cells at the end of the study (27, 28). The authors suggest that this cell death occurs at a much more rapid pace than expected due to telomere shortening alone, supporting the idea that imetelstat sodium may have additional mechanisms of action, such as effects on other cellular targets (e.g., casein kinase II signaling) (8). Imetelstat sodium preexposure also diminished the ability of a single MCF7-derived CSC to generate mammospheres and therefore decreased the capacity for self-renewal from 42% to 19% ($P = 0.0064$) (28). Imetelstat sodium was shown to be effective in inhibiting telomerase activity in drug-resistant adenocarcinoma NCI/ADR-RES cells (25).

Short-term exposure to imetelstat sodium (1 μM) induced nearly complete inhibition of telomerase activity within 3-4 days in the human lung cancer cell line A549-Luc. Inhibition was maintained for up to 3 days following dosing. Long-term exposure of the same cells to imetelstat sodium every 3 days for 12 weeks resulted in a decrease in growth rate within 3-4 weeks. At the end of the study, telomerase length had decreased by 45%. In the in vitro tumorigenicity assay model (anchorage in soft agar), the ability of the A549-Luc cells to form colonies was markedly reduced by long-term imetelstat sodium administration (23). Similar effects with a similar time course have been noted in other non-small cell lung cancer (NSCLC) cell lines (NCI-H157, H2087 and H1819 cells) (29-31). Interestingly, A549-Luc cells rapidly changed morphology following preexposure to imetelstat sodium, which could not be due to telomere shortening because of the rapid effect of administration. Follow-up studies confirmed that these changes were related to a dysfunction in cell adhesion, as evidenced by a 50% reduction in cellular attachment and a threefold decrease in total cell spreading surface area. Plating the

cells on type I collagen-coated surfaces prevented the action of imetelstat sodium and rescued cell adhesion, suggesting that telomerase shorting is not the sole mechanism by which imetelstat sodium mediates its effects (32, 33). In further support of imetelstat sodium affecting cell adhesion, proliferation and colony formation independently of telomere shortening, the expression of microtubule proteins such as actin and tubulin was significantly decreased within 24 hours of imetelstat sodium administration in A549 cells. Concomitant with these decreases, reversible perturbations in the cellular localization of microtubules have been noted, and following week-long exposure to the drug, altered expression of genes involved in cell cycle regulation, such as *CDK6* (cyclin-dependent kinase 6), *CDK4* (cyclin-dependent kinase 4) and *CCND1* (cyclin D1), was uncovered (34).

More recent investigations in a panel of NSCLC cell lines with various initial telomere lengths have indicated that the efficacy of imetelstat sodium to inhibit colony growth is not universal, although inhibition rates of 97% were observed in some cell lines. Two NSCLC cell lines (NCI-H1819 and NCI-H157) with initially long telomeres (> 14 kilobases) were particularly resistant to imetelstat sodium therapy. In these cells, telomerase was inhibited and telomere shortening occurred concomitant with reduced colony formation, but cell proliferation was not affected (31, 35). These data suggest a 3-responder protocol (responders, intermediates and nonresponders with > 70%, 20-70% and < 20% inhibition, respectively). This work is currently being extended to identify biomarkers present in these NSCLC responder groups that could prove useful as predictors of treatment response or in considering therapeutic regimens in which imetelstat sodium is used in combination with other treatments (31, 36).

In the human prostate cancer cells DU 145, PC3, C42 and LNCaP and in the CSCs derived from these cells, imetelstat sodium inhibited telomerase activity in a concentration-dependent manner and induced telomere shortening, leading to decreases in cell proliferation and eventually cell death (1, 37). Imetelstat sodium has also proven effective in significantly inhibiting telomerase activity, shortening telomere length and ablating colony formation in the human pancreatic cancer cell line PANC-1 and PANC-1-derived CSCs (28). In primary human glioblastoma-derived CSCs, imetelstat sodium inhibited telomerase activity in a concentration-dependent manner (IC_{50} = 0.45 μM), which coincided with gradual telomere shortening, reduced rates of proliferation, and eventually cell death (38). In INA6 and ARP cell models of multiple myeloma (MM), telomerase inhibition was achieved within 6 hours following the application of 1 μM imetelstat sodium. In INA6 cells, a 100% decrease in viability was observed following a 3-week exposure protocol. For ARP cells, which possess longer telomeres, apoptosis and complete cell death occurred within 5 weeks at a higher imetelstat sodium concentration of 2 μM. In both cell populations, imetelstat sodium induced telomere shortening (39-41). In CSCs derived from human MM cell lines (RPMI 8225, NCI-H929 and U266), imetelstat sodium (0.5-1.0 μM) markedly reduced telomerase activity within 48 hours and reduced the self-renewal and clonogenic capacity of the cells within 5 weeks (42, 43). Finally, in a panel of ovarian carcinoma cell lines, imetelstat sodium inhibited telomerase activity by > 95% and induced apoptosis with an IC_{50} of 1.97 μM (44).

In cells cultured ex vivo from patients with T-cell prolymphocytic leukemia, imetelstat sodium (0, 1, 3 and 10 μM) elicited significant cytotoxicity and an increase in apoptotic markers in a concentration-dependent fashion (N = 4; P = 0.008) (45). Similar effects were noted in CSCs derived from primary cells from patients with MM (42).

Murine xenograft models of tumor and metastasis have been used extensively to study the efficacy of imetelstat sodium in reducing tumor growth in vivo. Immunodeficient mice were implanted with A549 cells that had been preexposed to imetelstat sodium (1 μM every 3 days for 3 weeks) and A549 cells that had not (control cells). Subsequently, the mice received imetelstat sodium (5 mg/kg i.p. every 3 days for 3 weeks). In the imetelstat sodium-treated mice with control implants, lung metastasis was observed at 3-4 weeks after implantation, while no metastasis occurred in the imetelstat sodium-treated mice with implants of the imetelstat sodium-preexposed cells. In the same mouse model without preexposure, imetelstat sodium reduced in vivo tumor formation in a dose-dependent manner (23). Furthermore, in another A549 xenograft model, imetelstat sodium (15 and 36 mg/kg) induced highly significant, dose-dependent tumor growth inhibition of 38% and 72%, respectively (46).

MDA-MB-231 breast cancer cells were xenografted into athymic nude mice to investigate the effects of imetelstat sodium (30 mg/kg i.p. every 3 days for 4 weeks). The lung tissue of imetelstat sodium-treated mice exhibited significantly fewer tumor nodules when compared with saline-treated controls (25). Imetelstat sodium significantly retarded glioblastoma tumor growth (P = 0.01) and increased survival in mice with implants of human brain glioma U-251 MG cells. Furthermore, direct injection of imetelstat sodium into the implant prevented the establishment and growth of the tumor (47). Xenograft models have also been utilized to study imetelstat sodium effects on ovarian cancers in vivo. Using a retroviral delivery system, human ovarian cancer OVCAR-3 cells were implanted into immunodeficient mice that received imetelstat sodium at 30, 15 or 5 mg/kg i.p. twice weekly for 4 weeks (N = 6). The lower dose had no effect but the higher doses resulted in a 50% decrease in tumor volume (P = 0.003) (44).

In an in vivo model human hepatocellular cancer Hep 3B cells were implanted into nude mice. Imetelstat sodium was administered when tumors became evident. Treatment caused a sixfold (P = 0.04) reduction in telomerase activity, reduced proliferation by 20.5% (P = 0.007), induced apoptosis and reduced tumor growth, improving survival in a dose-dependent manner (48-50).

More recently, Hsd nude mice were implanted with pancreatic cancer PANC-1 cells. Prior to being grafted, the cells were exposed to the drug or saline for 45 days. Animals were grouped as those receiving saline-preexposed cells and saline injections (group 1), imetelstat sodium-preexposed cells and saline injections (group 2) or imetelstat sodium-preexposed cells and imetelstat sodium (30 mg/kg i.p. every 3 days for 4 weeks) injections (group 3). On day 46, the tumor engraftment rates were 100%, 50% and 40%, respectively, demonstrating that both pre- and post-graft administration of the drug significantly decreased the percentage of CSCs within the grafted cell populations and that post-treatment administration further reduces tumorigenicity (28).

Researchers have also investigated the use of imetelstat sodium in treating MM in vivo. Imetelstat sodium produced > 90% inhibition concomitant with an increase in apoptosis in an MM xenograft model. In addition, imetelstat sodium (30 mg/kg i.p. three times weekly for 4 weeks) reduced tumor mass by 56% ($P < 0.001$) (51-53). More recently, two MM xenograft mouse models were used to study the drug in vivo. In the first, MM IA6 cells were injected into human fetal bone grafts that had been implanted into immunodeficient mice. The measurement of human soluble interleukin-6 receptor (IL-6R) in the serum was used as an indirect measurement of cancer cell growth. Treatment of these animals with imetelstat sodium (25-35 mg/kg i.p. b.i.d.) significantly reduced the level of receptor in the serum and treated mice showed a greater overall survival than the untreated controls. The same study reports a second xenograft model in which myeloma MM1S cells were subcutaneously inoculated in the interscapular space, resulting in the formation of palpable tumors. Daily administration of imetelstat sodium (45 mg/kg i.p.) for 3 weeks resulted in a significant reduction in tumor size (41). No treatment-related toxicities have been observed in any in vivo xenograft models studied to date.

In addition to producing significant inhibition of telomerase activity, colony formation and tumor growth as a single agent, imetelstat sodium has been shown to act synergistically with chemo- and radiotherapies. MM cells preexposed to imetelstat sodium (1 μM) developed an increased sensitivity to growth arrest induced by the heat shock protein HSP 90 inhibitor tanespimycin (17-AAG; 0.05 μM) (39). In a 24-week investigation, imetelstat sodium increased the sensitivity of the drug-resistant NSCLC cell line NCI-H1819 to a combination of carboplatin and paclitaxel by week 16 (29, 30). In prostate cancer cell lines, the chemotherapeutic agents docetaxel and doxorubicin did not show any increase in efficacy in relation to imetelstat sodium-induced telomerase inhibition. However, an improved anticancer potential for both docetaxel and doxorubicin correlated with imetelstat sodium-induced telomere shortening (37). The anticancer drug paclitaxel demonstrated synergistic action with imetelstat sodium in a breast cancer cell line and in in vivo models (26). Furthermore, imetelstat sodium has been shown to increase the sensitivity of drug-resistant forms of breast cancer to the monoclonal antibody trastuzumab (54, 55).

Recent evidence suggests that inhibition of serine-protein kinase ATM (ataxia telangiectasia mutated) alongside imetelstat sodium treatment can synergistically increase the cytotoxicity induced by etoposide, in a cell cycle-dependent manner, in breast and colorectal cancer cell lines (53). In an in vivo human MM xenograft mouse model, the use of imetelstat sodium in combination with melphalan was more effective than either agent alone and inhibited tumor growth by 68% (56). Furthermore, when tested in various cancer xenograft models, the efficacy of both bortezomib and paclitaxel was improved by combination therapy with imetelstat sodium (57). In a human ovarian cancer SK-OV-3 xenograft model in mice, a combination of cisplatin and imetelstat sodium demonstrated significant antitumor activity, in striking contrast to either agent used alone (46). Finally, the telomere shortening properties of imetelstat sodium have been shown to increase radiosensitivity in breast cancer MDA-MB-231 cells and in mouse xenograft models. Inhibition of breast cancer cell growth was improved by up to 30% ($P = 0.01$) in vitro, and tumor growth in vivo was synergistically reduced (58, 59).

PHARMACOKINETICS AND METABOLISM

Studies in cynomolgus monkeys demonstrated that imetelstat sodium at a dose of 5 mg/kg infused for 6 hours attained maximal plasma concentrations (C_{max}) of ~30-60 μg/mL. At 10 mg/kg over 6 hours, concentrations were ~90-115 μg/mL and it was well tolerated, with < twofold increases in activated partial thromboplastin time (aPTT) and no significant complement activation. Plasma half-life ranged from 2.9 to 5.3 hours with doses of 5-15 mg/kg. The relatively long half-life of the drug predicts that within the dose range of 5-15 mg/kg, the concentration in plasma will remain above 10 μg/mL for more than 12 hours, which is consistent with the target tissue concentration required to attain 50-80% telomerase inhibition (60, 61). In pharmacodynamic experiments in mice, target inhibition from single doses was long-lasting (> 7 days) (61). In both rats and humans, the efficacy of telomerase inhibition can be assessed in a noninvasive manner by collecting samples of hair follicles. Imetelstat sodium elicited sustained concentration-dependent inhibition of the robust telomerase activity in the hair follicles of rodents and humans, as assessed by the telomeric repeat amplification protocol (TRAP) assay (62, 63).

SAFETY

The attractiveness of imetelstat sodium as an anticancer agent resides predominantly in its mechanism of action. Since telomerase is not expressed to any significant level in postnatal somatic cells but is highly expressed in bulk cancerous cells and CSCs, its anticancer potential is highly specific. In all preclinical evaluations, imetelstat sodium successfully induced apoptosis and cell death of cancerous cells without inducing cytotoxicity in noncancerous cells. In patients, imetelstat sodium is generally well tolerated and mild adverse events (AEs) (grade 1-2) have included activated partial thromboplastin time (aPTT) prolongation, nausea, vomiting, fatigue, diarrhea, anemia, mild anorexia, elevated γ-glutamyltransferase and peripheral neuropathy (64-66). Dose-limiting toxicities related to imetelstat sodium include decreases in white blood cell (neutropenia) and platelet counts (thrombocytopenia), particularly in patients who had previously received a high number of pretreatments and in those on higher doses of imetelstat sodium (65-67).

CLINICAL STUDIES

Following promising preclinical efficacy, imetelstat sodium was advanced into phase I/II trials to assess dosage, efficacy, safety and tolerability.

Three phase I studies have been completed (68-70), and data from one are available. The first was a dose-escalating phase I investigation to determine the safety, maximal tolerated dose and pharmacokinetics of imetelstat sodium in patients with relapsed and refractory MM (68). Twelve patients were split into 3 cohorts and received 3 weekly 2-hour intravenous injections of imetelstat sodium at 3.2, 4.8 or 7.2 mg/kg. Treatment-related AEs were generally mild and registered at grade 1 or 2, and are discussed in the safety section. The post-infusion plasma concentrations (C_{max}) showed a linear relationship with dose. The mean plasma concentrations declined 41.1 ± 17.6% over a 2-hour post-injection period (68, 69).

Currently, an active phase I study is investigating safety and dosing in patients with chronic lymphoproliferative disease (71). A second active phase I study is a dose-escalating investigation examining the safety, tolerability, and maximal tolerated dose of imetelstat sodium in patients with refractory or relapsed solid tumors (72). The 20 patients enrolled received a 2-hour infusion of imetelstat sodium at 0.4-4.8 mg/kg/week. As with the data from the previous study, most AEs were grade 1 or 2 and are discussed in the safety section. The plasma half-life was measured at 4-5 hours. Following this dosing procedure, the maximal tolerated dose was determined to be > 3.2 mg/kg/week (65, 73). Data from the extension and enrollment of more patients in this study were also presented at a recent conference. Patient cohorts received imetelstat sodium (4.8, 6.0, 7.5, 9.4 or 11.7 mg/kg/week as a 2-hour i.v. infusion). Overall, following this dose regimen, the exposure and drug plasma concentrations of imetelstat sodium were consistent with efficacy measurements from preclinical in vivo models. In addition, hair follicles were collected from nine patients to assess telomerase activity. Successful telomerase inhibition occurred within 24 hours of infusion. In one patient receiving imetelstat sodium at 6 mg/kg/week, > 60% inhibition of telomerase activity was noted within 24 hours. The conclusion of the study was that rather than weekly dosing at 3.2 mg/kg/week, a dose of 9.4 mg/kg given on an intermittent dosing schedule (days 1 and 8 of a 21-day cycle) would be the recommended dose for single-agent phase II studies of imetelstat sodium (65).

This once-monthly (every 28 days) dose regimen was then further assessed. Patients received imetelstat sodium as a 2-hour intravenous infusion at 9.4 or 11.7 mg/kg (n = 3 and 13, respectively) on day 1 of a 28-day cycle. Treatment-related AEs were mostly considered mild (grade 1-2), and treatment was well tolerated. Significant interindividual pharmacokinetic variability was seen in those on the higher dose (C_{max} = 190 ± 69 µg/mL; AUC = 1698 ± 617 µg/h/mL). Moreover, in leukocytes from three patients in the higher-dose group, telomerase activity was inhibited by 33-72% (66).

Another two phase I trials are recruiting to investigate the potential of imetelstat sodium in treating solid tumors in young patients (74), and in combination with trastuzumab in patients with drug-resistant receptor tyrosine-protein kinase erbB-2 (HER2)-positive breast cancer (75).

A phase I/II study investigating the use of imetelstat sodium in combination with paclitaxel and bevacizumab to treat patients with locally recurrent or metastatic breast cancer has reached completion (76). Results from his study were presented at the 2010 annual meeting of the American Society of Clinical Oncology (ASCO). Individuals were divided into four cohorts (n = 4) receiving imetelstat sodium (160, 240, 300 or 375 mg/m^2 i.v. on days 1, 8 and 15) with paclitaxel (90 mg/m^2 i.v. on days 1, 8 and 15) and bevacizumab (10 mg/kg i.v. on days 1 and 15). Treatment was generally well tolerated, with only mild AEs in the first cycle. Samples for pharmacokinetic analysis were retrieved from three subjects in each cohort. Using response evaluation criteria in solid tumors (RECIST) v.1 scoring, the best overall response rate was 53.8% (95% confidence interval: 28.7-77.6). The median duration of response was 21.7 weeks. Single-dose kinetics showed dose-dependent increases in exposure up to 300 mg/m^2 with a half-life of 4-5 hours. The pharmacokinetic profile of imetelstat sodium was unchanged when administered as a combination therapy with paclitaxel and bevacizumab (77).

The phase II stage of the phase I/II study mentioned above is currently under way to assess the pharmacodynamics of telomerase inhibition in combination therapy (77). An additional four phase II studies are currently recruiting: an open-label study to evaluate the activity of imetelstat sodium in patients with essential thrombocythemia (78); imetelstat sodium as maintenance therapy after initial induction chemotherapy in NSCLC (79); imetelstat sodium in combination with paclitaxel (with or without bevacizumab) in patients with locally recurrent or metastatic breast cancer (80); and an open-label study to determine the effect of imetelstat sodium in patients with previously treated MM (81).

SOURCE

Geron (US).

DISCLOSURES

The author states no conflicts of interest.

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