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MONOGRAPH

LOR-2040

Antisense Oligonucleotide Targeting RRM2
Oncolytic

GTI-2040 (former code name)
NSC-722929

20-Mer phosphorothioate antisense oligonucleotide that specifically targets ribonucleotide reductase subunit M2 (RRM2), whose sequence is: 5'-GGCTAAATCGCTCCACCAAG-3'

EN: 277748

ABSTRACT

LOR-2040 (formerly GTI-2040), an antisense oligonucleotide (ASO) developed by Lorus Therapeutics, is currently undergoing clinical evaluation for the treatment of a variety of tumors, including acute myeloid leukemia, metastatic breast cancer, colon, renal and non-small cell lung cancer. LOR-2040 acts by specifically targeting the M2 subunit of ribonucleotide-diphosphate reductase (RRM2), an enzyme that is instrumental in DNA synthesis and cell proliferation. RRM2 overexpression has been implicated in tumor progression and the development of malignancy and LOR-2040-mediated downregulation of RRM2 may therefore prove beneficial in cancer therapy. ASO technology offers the possibility of silencing the expression of disease-causing genes in a clinical setting, and as such may represent a means for specific, rational drug design for disease treatment at the molecular level.

BACKGROUND

Antisense oligonucleotide (ASO) technology has emerged as a promising therapeutic modality that offers the possibility of selectively modulating the expression of genes involved in the pathogenesis of malignancies and other genetic diseases. Antisense therapy represents a novel genetic-based rational drug design approach based on the silencing of disease-causing gene expression in clinical settings. ASOs are single-stranded deoxyribonucleotide sequences (typically 18-21 nucleotides in length) that are able to bind to the target messenger RNA (mRNA) via sequence-specific Watson-Crick hybridization, resulting in an ASO–mRNA heteroduplex. The formation of this heteroduplex leads to downregulation of target protein expression, most frequently through a mechanism involving mRNA degradation by ribonuclease (RNase) H, leaving the ASO component of the heteroduplex intact. Additional mechanisms implicated in ASO-induced protein knockdown include translational arrest by steric hindrance imposed on the ribosome by the ASO–mRNA heteroduplex, inhibition of mRNA splicing and destabilization of pre-mRNA in the nucleus (1). Due to the susceptibility of unmodified ASOs to degradation by cellular nucleases, a number of chemical modifications, such as a phosphorothioate-modified backbone (first-generation ASOs), 2′-alkyl ribose modifications of phosphorothioate oligonucleotides (second-generation ASOs) and chemical modifications of the furanose ring (third-generation ASOs), have been devised to improve nuclease resistance, prolong tissue half-life and enhance target affinity and potency, while reducing non-sequence-specific toxicity. Phosphorothioate ASOs are the best-characterized class of oligonucleotides, most ASOs currently in clinical evaluation being first-generation phosphorothioate-modified compounds designed to inhibit gene expression via an RNase H-based mechanism (2).

LOR-2040 (formerly GTI-2040; Lorus Therapeutics) is a 20-mer phosphorothioate-modified ASO that binds to the mRNA encoding the M2 subunit of ribonucleotide-diphosphate reductase (RRM2), an enzyme essential for DNA synthesis and cell proliferation. RRM2 catalyzes the reduction of ribonucleotides to deoxyribonucleotides in the rate-limiting step of DNA synthesis. RRM2 is elevated in many tumor types and is thought to play a role in tumor progression as a signal molecule in a molecular pathway important in determining malignancy (3). LOR-2040 has been characterized in a number of in vitro and in vivo studies and is currently undergoing clinical evaluation for a wide range of cancer types, including metastatic breast and colon cancer, acute and chronic myeloid leukemia (AML/CML), myelodysplasia, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC). LOR-2040 has received orphan drug designation from the FDA for the treatment of RCC. Orphan drug designation was also assigned to the drug by both the FDA and the E.U. for the treatment of AML (4).

PRECLINICAL PHARMACOLOGY

In vitro investigation of the ability of LOR-2040 to alter nucleoside triphosphate levels by inhibiting the expression of RRM2, an enzyme upregulated in almost all cancer types, was performed in K-562 human leukemia cells using liquid chromatography–mass spectrometry. LOR-2040 delivered to the cells either by electroporation or NeoPhectin™-based transfection (60-70% efficiency for both methods) downregulated both RRM2 mRNA and protein levels in a

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concentration-dependent manner at 24 h by inducing a significant reduction in the amount of dATP and dCTP (approximately 2-fold; $P < 0.05$), without having an effect on the levels of other nucleoside triphosphates (5).

In the NSCLC cell line NCI-H460, exposure to LOR-2040 for 4 h followed by 18-h incubation resulted in a significant decrease in RRM2 mRNA levels that was reflected in a reduction in both the steady-state level and the biosynthetic rate of RRM2 protein. At 72 h after LOR-2040 application, RRM2 protein levels returned to normal. The target-selective mechanism of action of LOR-2040 was demonstrated in the human metastatic melanoma A2058 cell line, where it decreased the expression of RRM2 mRNA without affecting the transcripts for β-actin, signal recognition particle or RNase P, as detected by Northern blot analysis. LOR-2040 also displayed good antiproliferative activity in colony-forming assays against a wide range of cancer cell lines in a concentration-dependent and saturable manner, with the maximal effect seen at a concentration of 2 μM (6).

Evaluation of the combined administration of LOR-2040 and docetaxel, either sequentially or concurrently, revealed that the greatest effect of combination treatment was achieved when docetaxel was applied at 48 h after LOR-2040 transfection in the human NCI-H460 and A549 NSCLC cell lines (7). Application of LOR-2040 (10 μM for 24 h) followed by the nucleoside analogue cytarabine (ara-C; 10-20 μM) to K-562 cells induced downregulation of RRM2 and a 40% decrease in the levels of dCTP, dTTP and dATP at 48 h compared with control cells ($P < 0.05$) (8).

In vivo LOR-2040 showed significant and sequence-specific antitumor activity in mice with palpable tumors caused by injections of murine R3 fibrosarcoma or human renal carcinoma Caki-1 and A-498 cell lines. Similar sequence specificity, as indicated by the inactivity of mismatched and scrambled control ASOs, was observed following administration of LOR-2040 to mice bearing human hepatocellular carcinoma Hep G2 tumor xenografts. In mice bearing human renal Caki-1 and A-498 xenografts LOR-2040 displayed antitumor activity that was superior to fluorouracil, gemcitabine and vinblastine. Administration of LOR-2040 to SCID mice bearing active Burkitt's lymphoma produced an increase in survival time of up to 72 days following treatment cessation, with concomitant evidence of recovery from lymphoma-associated symptoms. In an experimental model of metastasis, pretreatment of murine R3 fibrosarcoma and human C8161 melanoma cells with 0.2 μM LOR-2040 prior to tail vein injection in mice resulted in a significant reduction in the extent of lung nodule formation in these animals. Treatment with LOR-2040 after tumor cell injection was also associated with a decrease in the number of developing lung nodules compared with saline-treated mice (9).

In the murine NCI-H460 xenograft model, sequential treatment with docetaxel at 48 h following LOR-2040 administration demonstrated potent antitumor activity, with synergistic effects on the induction of cell cycle arrest and apoptosis seen on the 48-h treatment schedule (7). Synergistic antitumor effects of LOR-2040 with the immunotherapeutic compounds interleukin-2 (IL-2) and interferon alfa, respectively, were also observed in the murine Caki-1 and the Caki-1 and A-498 tumor xenograft models. Synergistic effects of IL-1 and interferon alfa with LOR-2040 were seen at intermediate doses, whereas complete tumor regression was observed at higher doses. Immunohistochemical analysis of tissues derived from these animals revealed a high percentage of cells undergoing apoptosis, which was paralleled by a reduction in cellular proliferation (10).

PHARMACOKINETICS AND METABOLISM

A study to investigate the population pharmacokinetics of LOR-2040 in the plasma and peripheral blood mononuclear cells (PBMCs) of patients with AML identified cell density and/or cell type as determining factors of the plasma clearance and cellular uptake of the compound. Relapsed or refractory AML patients (N = 35) who had received LOR-2040 as a continuous i.v. infusion (7 mg/kg/day) for 144 h in combination with a high dose of ara-C during a phase I trial were evaluated in this study. A positive correlation between bone marrow cellularity and plasma clearance of LOR-2040 was reported. Uptake of the compound in PBMCs was consistent, with an active transport mechanism from the central to an intracellular compartment based on measurements of the Michaelis-Menten constant (K_m) and the maximum rate of metabolism (V_{max}). Gender and white blood cell counts were identified as important covariates of K_m and V_{max} values (11).

Characterization of the plasma pharmacokinetics and metabolism of LOR-2040 and determination of intracellular levels in red blood cells (RBCs), PBMCs and bone marrow mononuclear cells using a validated ultrasensitive and specific hybridization–ligation enzyme-linked immunosorbent assay technique was performed in plasma, urine, PBMC and bone marrow samples derived from 11 AML patients receiving a continuous infusion of LOR-2040 (5 mg/kg/day for 6 days). The plasma pharmacokinetics of the compound were best described by a two-compartment infusion model; sustained drug levels were 2.7-fold higher in bone marrow than in plasma. A high level of plasma protein binding was detected (> 99.9%) at concentrations of < 1 μM. Urinary excretion of LOR-2040 was low (< 0.1% of dose recovered in 24 h) and no chain-shortened metabolites were detectable in urine (12).

Administration of LOR-2040 as a continuous i.v. infusion for 144 h at 3.5 mg/kg/day (low dose; LD) or 5 mg/kg/day (high dose; HD) to AML patients (n = 6/dose group) provided mean steady-state plasma concentrations of 239 and 353 nM, respectively, in the LD and HD groups. A biphasic decline in drug levels was observed in PBMCs, with sustained levels of 15.6 and 5.5 nM, respectively, at 24 and 48 h after cessation of infusion. Downregulation of RRM2 was detected in one and five patients receiving LD and HD LOR-2040, respectively (13).

SAFETY

Good laboratory practice toxicology studies of LOR-2040 performed in rodents and nonhuman primates (monkeys) indicated a toxicokinetic profile typical of a phosphorothioate oligonucleotide. The data obtained from these analyses suggested that LOR-2040 may be safe in humans at concentrations exceeding therapeutic doses (14).

CLINICAL STUDIES

Pharmacodynamic analysis of levels of deoxyribonucleotide triphosphates (dNTPs), ribonucleotide triphosphates and ara-C levels in

bone marrow cells derived from four patients with refractory/relapsed AML administered LOR-2040 (3.5 or 5 mg/kg/day by continuous i.v. infusion for 6 days) plus a high dose of ara-C infused on days 2-6 in a phase I study demonstrated an inverse correlation between dCTP, dATP and dTTP levels ($P < 0.1$, $P < 0.05$ and $P < 0.05$, respectively) and an increase in the accumulation of ara-CTP. A linear correlation between a decrease in dCTP and a reduction in RRM2 protein levels was observed ($P < 0.05$). The data indicated the possibility that LOR-2040 may enhance the antileukemic activity of ara-C by decreasing the activity of ribonucleotide-diphosphate reductase, thus reducing the levels of endogenous dNTPs, which ara-C competes against for incorporation into DNA (8).

In a dose-escalating phase I trial sponsored by the Cancer Therapy Evaluation Program (CETP), LOR-2040 was administered as a continuous i.v. infusion at a starting dose of 3.5 mg/kg/day (days 1-7) followed by ara-C (2-h infusion of 2 g/m^2/dose every 12 h on days 2-7) in adult patients with AML (15, 16). Following an event of grade 3 cerebellar toxicity, the protocol was amended to a dose of 3.5 or 5 mg/kg/day LOR-2040 (days 1-6) combined with 2.5 or 3 g/m^2/dose ara-C on days 2, 4 and 6 or 2, 3, 4 and 6. The maximum tolerated dose (MTD) in this trial was 5 mg/kg/day LOR-2040 coadministered with 3 g/m^2/dose ara-C every 12 h for eight doses, with neurotoxicity being the dose-limiting factor. Bone marrow levels of RRM2 were reduced by > 50% at 24 and 120 h. A higher bone marrow intracellular concentration of the compound was detected at 120 h compared with 24 h, which suggested intracellular drug accumulation over time. Complete remission was achieved by 35% of patients, which correlated with higher baseline RRM2 levels ($P = 0.03$) and RRM2 decreases at 24 h following LOR-2040 treatment ($P = 0.04$) (16). Toxicity profiles were similar for the combination treatment and ara-C therapy alone. Grade 3-4 nonhematological toxicities included fatigue, fever, anorexia, pneumonitis and catheter-related infections. The trial demonstrated the feasibility of the combination of LOR-2040 with ara-C for the treatment of AML (17). In the same trial, the younger cohort (18-59 years of age), which received a dose of 3.5 mg/kg/day LOR-2040 (days 1-6) combined with ara-C (every 12 h i.v. on days 2, 4 and 6), displayed higher AUC and half-life values. Complete remission seen in this cohort correlated with a higher nuclear concentration of LOR-2040 (62% vs. 21.2% in the cytoplasm) and robust RRM2 downregulation compared with nonresponders. No responses were seen in patients in the older cohort (≥ 60 years of age) (18).

Patients with advanced cancer, including colon, renal, pancreatic, lung and liver carcinoma, mesothelioma, lymphoma or sarcoma, were enrolled in a phase I trial aiming to assess a continuous i.v. infusion of LOR-2040 on a 21-day cycle of treatment followed by 1 week of rest. The starting dose of LOR-2040 was 18.5 mg/m^2/day, which was subsequently doubled in cohorts of one to three patients until the incidence of grade 1 toxicity. Escalation of 20-30% was subsequently evaluated in cohorts of at least three subjects. Dose-limiting toxicities (DLT) were established as grade 4 neutropenia lasting ≥ 3 days or with concomitant fever, grade 4 thrombocytopenia, grade 3 thrombocytopenia with ≥ grade 1 bleeding or nonhematological toxicity (≥ grade 3) despite maximal supportive care (19). In this trial 36 patients received 49 cycles of treatment at doses ranging from 18.5 to 222 mg/m^2/day at six dose levels. LOR-2040 was well tolerated. Frequent grade 1-2 toxicities included fatigue (69%), anorexia (42%) and nausea (38%) (20). At the highest dose level, two patients experienced reversible dose-limiting hepatic toxicity. No complete or partial objective tumor responses were observed in this trial. Stable disease was achieved by four patients after two treatment cycles. The phase II recommended dose was established as 185 mg/m^2/day (21).

A phase I/II study aiming to determine the recommended phase II dose (RP2D) of LOR-2040 in combination with docetaxel as second-line therapy in patients with advanced NSCLC evaluated escalating doses of LOR-2040 administered as 14-day continuous i.v. infusions, with docetaxel given i.v. once every 21 days. The RP2D established in this study was LOR-2040 5 mg/kg by continuous i.v. infusion for 14 days plus docetaxel at 75 mg/m^2 i.v. once every 21 days (22). The study reported no DLT at any dose level. Toxicities associated with the combination therapy included neutropenia, neutropenic sepsis, fatigue and gastrointestinal toxicities. In a total of 23 patients receiving treatment, stable disease, including minor response, was noted in 2, 2 and 6 patients at the first, second and RP2D dose levels, respectively (23).

An open-label, nonrandomized trial was conducted in patients with metastatic RCC to assess the toxicity and determine the objective response rate of LOR-2040 in combination with capecitabine (24). Patients with metastatic RCC were treated with oral capecitabine (1660 mg/m^2) and LOR-2040 (148 or 185 mg/m^2/day by continuous i.v. infusion) for 21 days of each 28-day cycle (25). In the phase I part of this trial, DLT (grade 3 diarrhea) was seen in one of six subjects treated with 185 mg/m^2/day LOR-2040 but in none of the three patients treated with the lower dose (148 mg/m^2/day). One patient receiving the highest dose in the phase I portion of the trial, but none in the phase II part of the study, exhibited an objective response and therefore further accrual was suspended. The median time to progression was estimated to be 3.1 months and median survival was 12.1 months. The combination of LOR-2040 with capecitabine for the treatment of metastatic RCC was not recommended for further evaluation at the doses and schedules tested in this trial (26).

The efficacy of the combination of LOR-2040 with docetaxel and prednisone as first-line treatment in hormone-refractory prostate cancer (HRPC) was evaluated in a phase II trial by assessing the prostate-specific antigen (PSA) response rate. HRPC patients (N = 24) with adequate renal, hepatic and hematological function and no prior chemotherapy received LOR-2040 (5 mg/kg/day by continuous i.v. infusion for 14 days), docetaxel (75 mg/m^2 i.v. every 21 days) and prednisone (5 mg p.o. b.i.d.) (27). PSA responses were seen in 9 of 22 evaluable patients. Partial response and stable disease were observed in one and nine patients, respectively, whereas progressive disease was seen in three subjects. The median time to progression was estimated at 17 weeks (28).

The MTD of LOR-2040 and its efficacy for the treatment of patients with relapsed, refractory or high-risk acute leukemia, high-grade myelodysplastic syndromes or refractory or blastic-phase CML will be investigated in a phase I trial sponsored by the California Cancer Consortium and the National Cancer Institute (NCI). The study is currently recruiting participants (29). A multicenter phase I study aiming to evaluate a combination regimen comprising LOR-2040, oxaliplatin and capecitabine for the treatment of patients with locally advanced or metastatic colorectal cancer or other solid tumors is

currently ongoing but not recruiting participants. The study was designed to determine the toxicity and pharmacokinetics of this regimen and to establish the MTD of oral capecitabine (30). The pharmacodynamic activity and overall response rate of the combination of LOR-2040 with a high dose of cytarabine in patients with refractory and relapsed AML are under evaluation in a phase II trial conducted by Lorus Therapeutics in collaboration with Ohio State University. The study, which is currently recruiting patients, will also assess the toxicity profile of early and delayed GTI-2040 treatment (31). An ongoing phase II trial sponsored by the California Cancer Consortium and the NCI is investigating the combination of LOR-2040 with capecitabine for the treatment of metastatic breast cancer; this study is no longer recruiting participants. The primary outcomes of this trial include response rate and duration, toxicity and pharmacokinetics (32).

SOURCE

Lorus Therapeutics, Inc. (CA).

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