Drugs of the Future 2008, 33(4): 310-315

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.04.1192992

Elesclomol

USAN

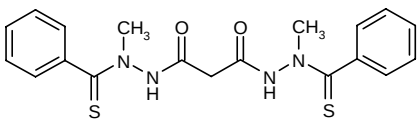
Apoptosis Inducer
Inducer of Oxidative Stress
HSP70 Inducer
Oncolytic

STA-4783

N'1,*N*'3-Dimethyl-*N*'1,*N*'3-bis(phenylthiocarbonyl)malonohydrazide

Propanedioic acid bis[2-methyl-2-(phenylthiocarbonyl)hydrazide]

InChI=1/C19H20N4O2S2/c1-22(18(26)14-9-5-3-6-10-14)20-16(24)13-17(25)21-23(2)19(27)15-11-7-4-8-12-15/h3-12H,13H2,1-2H3,(H,20,24)(H,21,25)



$C_{19}H_{20}N_4O_2S_2$
Mol wt: 400.5199

CAS: 488832-69-5

EN: 343476

Abstract

Elesclomol (STA-4783) is a small molecule that induces apoptosis via the mitochondrial apoptotic pathway in cancer cells by increasing oxidative stress, while having little or no effect on normal cells. The agent acts synergistically with established chemotherapeutic agents, including paclitaxel, to eradicate tumors in a range of human tumor xenograft models. Combination of elesclomol and paclitaxel was associated with little toxicity above that seen with paclitaxel alone in preclinical models and in a phase I trial. In a phase II trial in patients with metastatic melanoma, treatment with elesclomol in combination with paclitaxel doubled the mean progression-free survival relative to treatment with paclitaxel alone. Elesclomol is undergoing a phase III trial in combination with paclitaxel in patients with metastatic melanoma and it was recently awarded both orphan drug and fast track designations for this indication by the FDA. Additionally, the agent is being assessed in combination with paclitaxel and carboplatin in a phase I/II trial in patients with stage IIIb/IV non-small cell lung cancer (NSCLC).

Synthesis

Elesclomol can be prepared as follows. The precursor thiobenzoic acid *N*-methylhydrazide (III) can be obtained by either treatment of carboxymethyl dithiobenzoate (I) with methylhydrazine under alkaline conditions or by reaction of phenylmagnesium bromide (II) with carbon disulfide, followed by treatment with methylhydrazine. Then, dimerization of thiohydrazide (III) with malonic acid in the presence of DCC/HOBt, or with malonyl dichloride or malonic acid diphenyl ester, provides the target malonohydrazide derivative (1, 2). Conversion of elesclomol to different salts (including sodium, potassium, lithium, calcium, magnesium, ethanolamine and choline salts) has also been reported (3). Scheme 1.

Background

Melanoma is the most deadly form of skin cancer, and although it accounts for only about 4% of all newly diagnosed skin cancers, it causes about 80% of skin cancer-related deaths, and the incidence is on the rise in many countries. One of the reasons for the deadly nature of melanoma is its high metastatic potential and the poor prognosis for patients with metastatic melanoma; patients with stage I disease can be managed by surgery and adjuvant therapies and the 5-year survival rate is 90%, but the 5-year survival rate for patients with stage III/IV melanoma (metastatic) is generally < 50%, depending on the site of metastasis. Dacarbazine was approved for metastatic melanoma in 1975, although the response rates are only 10-20% and the median response duration is 4-6 months. High-dose bolus recombinant IL-2 (aldesleukin) has also been approved for this indication,

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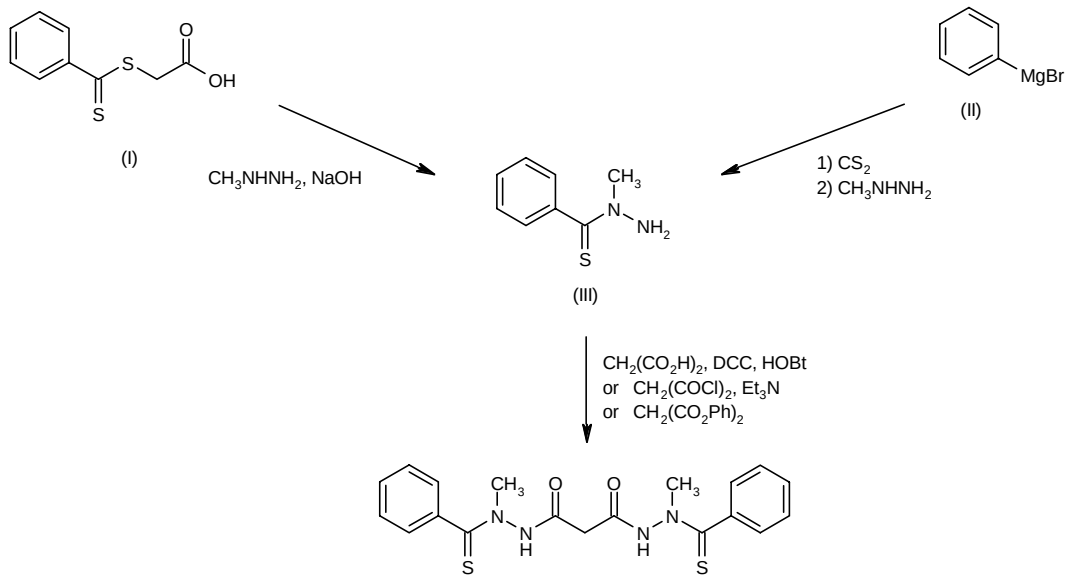
Scheme 1: Synthesis of Elesclomol



and although it has provided a durable response in some patients, there is no clear benefit in terms of overall survival and the treatment is very toxic. Thus, there is a need for new treatments that improve the survival and the quality of life of patients with metastatic melanoma (4, 5; www.melanomacenter.org, www.cancer.org).

Recent studies have indicated that under hypoxic conditions such as in tumor cells, mitochondria produce greater amounts of reactive oxygen species (ROS), and that beyond a certain point, ROS accumulation triggers apoptosis (6-8), indicating that agents that stimulate the production of ROS may have therapeutic potential in the treatment of cancer.

In vitro studies have shown that elesclomol (STA-4783) triggers selective apoptosis of cancer cells through a sequence of events starting with an increase in ROS, followed by increased levels of stress proteins such as heat shock protein 70 (HSP70) and oxidation of the mitochondrial lipid cardiolipin. Shortly after, the mitochondrial apoptosis pathway (cytochrome *c*- and caspase-9-dependent) is triggered, leading to cell death (9-11). Elesclomol has demonstrated strong anticancer activity in a broad range of preclinical models, including an increase in tumor-free survival and tumor eradication when used in combination with anticancer agents such as taxanes. The agent has been assessed in patients with solid tumors and in a phase I/II trial in patients with soft tissue sarcomas, and is being evaluated in a phase I/II trial in patients with non-small cell lung cancer (NSCLC). Elesclomol extended the time to disease progression in a phase II trial in patients with metastatic melanoma and is now being tested in a phase III trial in combination with paclitaxel for this indication. The FDA recently granted orphan drug status and fast track designation for its use in metastatic melanoma (12, 13).

Preclinical Pharmacology

Elesclomol was shown to induce the expression of ROS-regulated genes, including those for HSPs and metallothioneins, in cancer cells. Exposure to the agent resulted in the generation of ROS, followed by HSP70 induction, oxidation of cardiolipin in mitochondria, cytochrome *c* release from mitochondria, caspase activation and apoptosis; antioxidants were able to inhibit the induction of ROS, HSP70 and apoptosis (10, 11).

Elesclomol induced the expression of HSP70 in a wide variety of human cancer cell lines, including human breast carcinoma MDA-MB-435 cells at 0.1 μM, but not in normal cell lines such as human mammary epithelial cells or human renal epithelial cells at 5 μM. *In vivo*, elesclomol improved the antitumor activity of paclitaxel in murine xenograft models with the human tumors MDA-MB-435 (breast), MCF7 (breast), ZR-75-1 (breast), RERF (lung) and U-937 (lymphoma), without additional toxicity compared to paclitaxel alone. The improvement was dependent on the dose of elesclomol and there was no change in the pharmacokinetics of paclitaxel. Synergy was only observed *in vivo*, was absent in SCID-beige mouse xenograft models and tumor cells treated with elesclomol and expressing surface HSP70 (but not cells without surface HSP70) were lysed by mouse splenocytes, suggest-

ing a possible immune-mediated mechanism to account for the synergy (14).

Further studies in murine tumor models showed that elesclomol was active as a single agent and enhanced the activity of a range of anticancer agents, including paclitaxel (a microtubule stabilizer), docetaxel (a microtubule stabilizer), gemcitabine (a nucleoside analogue), rituximab (an anti-CD20 monoclonal antibody) and fractionated ionizing radiation. The models used included human melanoma, colon and lung tumors and lymphoma. Elesclomol was synergistic with paclitaxel in the syngeneic CT26 mouse colon carcinoma model in immunocompetent BALB/c mice. This combination was also synergistic in the M14 human melanoma xenograft model in T-cell-deficient nude mice and in the M14 xenograft model in B-, T- and natural killer (NK) cell-deficient beige-nude-Xid mice. As before, the synergy could not be explained by altered pharmacokinetics of paclitaxel, and the combination did not result in any further toxicity beyond that observed with paclitaxel alone. Elesclomol was synergistic with docetaxel in the M14 model; it enhanced the activity of gemcitabine in the RERF-LC-A1 human NSCLC and M14 xenograft models; it enhanced the activity of rituximab in the Daudi human Burkitt's lymphoma model; and it enhanced the activity of fractionated radiotherapy in the RERF-LC-A1 model (15).

Pharmacokinetics and Metabolism

Following a single i.v. dose of elesclomol alone or in combination with paclitaxel in rats and dogs, the AUC values for elesclomol were dose-proportional and the half-life was 40-50 min in rats and 1.2 h in dogs. Elesclomol did not affect the pharmacokinetics of paclitaxel in these animals. Studies with [^{14}C]-labeled elesclomol showed distribution to the kidney, lung and liver in rats and rapid elimination via the urine in rats (60%) and dogs (70%), with 80-90% of the drug and its metabolites eliminated within 48 h. Using *in vitro* systems, six metabolites could be detected, of which the three main inactive metabolites were the result of an exchange of one or both sulfur atoms for oxygen and hydrolysis of the C-N bond of the hydrazide portion of elesclomol. These same metabolites were observed in human plasma (16).

A phase I trial examined the pharmacokinetics of elesclomol in combination with paclitaxel in 35 adults with refractory solid tumors (17, 18). Patients received a starting dose of 135 mg/m^2 paclitaxel and 44 mg/m^2 elesclomol concurrently by i.v. infusion. For the second dose, paclitaxel was elevated to 175 mg/m^2 with the same dose of elesclomol, and then for all subsequent doses paclitaxel was held at 175 mg/m^2 and the dose of elesclomol was escalated from 44 to 525 mg/m^2 as permitted by dose-limiting toxicity (DLT). Treatment was every 21 days with a permissible 2-week extension to the dosing interval to allow recovery from DLTs up to a maximum of 6 cycles. Elesclomol exhibited apparent linear pharmacokinetics up to the dose of 438 mg/m^2. The compound was rapidly eliminated from plasma, with a half-life of 1.06 h, the mean clearance was 28.6 l/h/m^2 and the steady-state volume of distribution was 25.1 l/m^2. Higher doses of elesclomol reduced the clearance of paclitaxel, which was suggested to be responsible for the increase in toxicity seen on the combination at higher doses of elesclomol.

Safety

The toxicity of elesclomol was studied in mice, rats and dogs. Rats tolerated elesclomol at 125 mg/kg and the LD_{50} in rats and mice was > 200 mg/kg following i.v. injection, although some deaths were seen at this dose. Dogs tolerated elesclomol at 30 mg/kg and the LD_{50} was not reached (highest dose tested 37.5 mg/kg due to drug insolubility). There was no additional toxicity beyond that seen with paclitaxel alone when rats and dogs were treated with the combination (19).

The phase I trial in 35 patients with refractory solid tumors also examined the maximum tolerated dose (MTD) and toxicity profile of elesclomol in combination with paclitaxel (17, 18). At 175 mg/m^2 paclitaxel, grade 3/4 toxicities were seen in 13 patients at doses of elesclomol above 263 mg/m^2 and the MTD was established at 438 mg/m^2 elesclomol combined with 175 mg/m^2 paclitaxel. Dose-limiting adverse events were febrile neutropenia, mucositis and myalgia/arthralgia. The most frequent adverse events were fatigue (33%), myalgia/arthralgia (21%), neutropenia (21%), leukopenia (15%), neuropathy (9%) and mucositis (9%). Other possible treatment-related adverse events were anorexia, hyperglycemia, hypophosphatemia, candidiasis infection, abdominal pain, hypesthesia, pulmonary embolism and pruritic rash.

A phase I/II trial assessed the safety and efficacy of elesclomol in combination with paclitaxel and carboplatin in chemotherapy-naïve patients with advanced NSCLC (20). In this two-stage study, 16 patients were recruited to stage 1, consisting of two dosing cohorts: carboplatin AUC6, paclitaxel 175 mg/m^2 and elesclomol 233 mg/m^2 (n=7), or carboplatin AUC6, paclitaxel 200 mg/m^2 and elesclomol 266 mg/m^2 (n=9). Dosing was every 3 weeks for up to 6 cycles. No DLTs were observed in either cohort. The adverse events included arthralgia and myalgia, peripheral neuropathy, rash, nausea and vomiting, anorexia, fatigue, asthenia, alopecia, dyspnea, edema, dehydration, constipation, cough, anemia, leukopenia and neutropenia. The efficacy is described below (21, 22).

In a pooled safety analysis of all patients who have received elesclomol in combination with paclitaxel (n=239) *versus* those receiving paclitaxel alone (n=28), the most frequent adverse event attributable to elesclomol was neutropenia (6% *versus* 0 events in patients receiving paclitaxel alone); the frequency of fatigue, neuropathy and back pain was roughly comparable between the two groups (2-7%) and pain occurred in 2 patients in the paclitaxel + elesclomol group (< 1%) compared to 3 patients (11%) in the paclitaxel group (9).

Clinical Studies

In the phase I study of elesclomol in 35 patients with refractory solid tumors, of 24 evaluable patients, 2 heavily pretreated patients showed a partial response to therapy. Serum levels of HSP70 peaked at 8 h after dosing (17, 18).

In the phase I/II study evaluating the combination of elesclomol, carboplatin and paclitaxel, 6 patients achieved a partial response, 6 additional patients had disease stabilization and 7 of 8 showed increased natural killer (NK) cell activity. Stage 2 is a randomized (1:1), double-blind, parallel-assignment efficacy study. In this ongoing study, 87 patients received either carboplatin AUC6 + paclitaxel 200 mg/m^2 + elesclomol 266 mg/m^2 or carboplatin + paclitaxel without elesclomol. The primary endpoint is time to progression and the secondary endpoints are response rate, survival and quality of life (21, 22).

Another two-stage study is examining elesclomol in combination with paclitaxel in patients with refractory or recurrent soft tissue sarcomas (other than gastrointestinal stromal tumors, or GISTs) and with evidence of recent progression. Thirty patients were enrolled into stage 1 and received paclitaxel 80 mg/m^2 + elesclomol 213 mg/m^2 once weekly for 3 weeks of a 4-week cycle. The trigger for entry into stage 2 of the study (addition of a further 50 patients) was if at least 7 patients had stable disease or better or at least 2 patients had a partial response or better at 3 months. Fourteen of the 30 patients in stage 1 showed stable disease after 3 months and 54 additional patients were enrolled to stage 2. In a preliminary evaluation of 70 patients, 21 had disease stabilization after 3 months of treatment. Adverse events were typical for paclitaxel administered on a similar schedule, with fatigue, nausea, alopecia, anemia and diarrhea being the most common. No serious adverse events were attributed to elesclomol (23, 24).

Another phase I/II study evaluated elesclomol in combination with paclitaxel in patients with advanced metastatic melanoma (25). Stage 1 consisted of an initial safety assessment, with 3 patients receiving weekly paclitaxel 80 mg/m^2 + elesclomol 106 mg/m^2 for 3 weeks of a 4-week cycle, and 4 patients subsequently receiving paclitaxel 80 mg/m^2 + elesclomol 213 mg/m^2 on the same schedule. No DLTs were seen in either group and the higher dose was expanded to treat 20 patients. Adverse events were as expected for paclitaxel chemotherapy. An evaluation of 20 patients showed stable disease in 11 (a nonprogression rate of 55%) at 2 months, which met the prospectively chosen trigger point for initiation of stage 2 (a nonprogression rate of at least 50% at 2 months). Stage 2 was a double-blind, randomized, multicenter trial in which 81 patients with metastatic melanoma received either elesclomol plus paclitaxel (n=53) or paclitaxel alone (n=28) weekly for 3 weeks of a 4-week cycle. Patients in the control arm were allowed to cross over to the elesclomol arm upon disease progression. The primary endpoint of progression-free survival was 3.7 months in the paclitaxel + elesclomol treatment arm and 1.8 months in the paclitaxel arm in an intent-to-treat analysis. The response rate, a secondary endpoint, was 15.1% in the paclitaxel + elesclomol treatment arm and 3.6% in the paclitaxel arm. At 6 months, the percentage of patients free of disease progression was 35% in the elesclomol + paclitaxel arm and 15% in the paclitaxel arm, indicating a 42% reduction in the risk of disease progression in patients receiving the combination. A subgroup analysis showed that the progression-free survival among patients who had received no prior chemotherapy was 8.28 months for those receiving elesclomol + paclitaxel (n=23) and 2.4 months for those receiving paclitaxel alone (n=9); for those with one prior chemotherapy, the progression-free survival was 3.12 months in the elesclomol + paclitaxel arm (n=29) *versus* 1.77 months in the paclitaxel arm (n=19). Three patients who had rapid disease progression on paclitaxel alone (range: 1-1.7 months) showed a significant inversion of time to progression when switched to elesclomol + paclitaxel treatment (range: 2.3-5.5 months), suggesting a study drug effect. A retrospective analysis of overall survival showed that the median overall survival for patients who were randomized to elesclomol + paclitaxel was 12 months, and for those randomized to paclitaxel alone 7.8 months. However, in an analysis of all patients who received elesclomol + paclitaxel (including the 53 initially randomized to elesclomol and 19 who crossed over upon disease progression), the overall survival ranged from 12 to 14.3 months compared to 5.6 months in those who did not cross over to receive elesclomol (n=9). The elesclomol + paclitaxel combination was well tolerated and 10% of patients in the paclitaxel + elesclomol arm discontinued due to adverse events *versus* 14% in the paclitaxel arm. Adverse events of grade 3 or higher were similar in both treatment arms (54% with paclitaxel + elesclomol and 57% with paclitaxel alone), except for transient neutropenia seen in 4 patients in the elesclomol + paclitaxel arm *versus* no patients in the paclitaxel arm. Serious adverse events were neutropenia, back pain, fatigue and neuropathy. The most common adverse events were fatigue, alopecia, constipation, diarrhea, nausea, hypesthesia, arthralgia, insomnia and anemia, and the incidence was generally comparable between the two groups, suggesting that elesclomol increases the efficacy of treatment in this disease without substantially increasing toxicity (12, 13, 26-30).

Elesclomol has entered a phase III trial (the SYMMETRY trial) in patients with metastatic melanoma with the same treatment arms, dose and schedule as the above phase II trial (31). As previously, the primary endpoint is progression-free survival and the study is powered for overall survival as a secondary endpoint.

Sources

Synta Pharmaceuticals Corp. (US); developed under a global collaboration with GlaxoSmithKline (GB, US).

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