Effect of hypoxia on the expression of phosphoglycerate kinase and antitumor activity of troxacitabine and gemcitabine in non-small cell lung carcinoma

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Abstract
β-L-Dioxolane-cytidine (L-OddC; BCH-4556; troxacitabine), a novel L-configuration deoxycytidine analogue, was under clinical trials for treating cancer. The cytotoxicity of L-OddC is dependent on its phosphorylation to L-OddCTP by phosphoglycerate kinase (PGK) and its subsequent addition into nuclear DNA. Because PGK is induced with hypoxia, the expression of hypoxia-inducible factor-1α and PGK of H460 cells (human non-small cell lung carcinoma) in vitro and in vivo was studied. In culture, hypoxic treatment induced the protein expression of PGK by 3-fold but had no effect on the protein expression of other L-OddC metabolism-associated enzymes such as apurinic/apyrimidinic endonuclease-1, deoxycytidine kinase, CMP kinase, and nM23 H1. Using a clonogenic assay, hypoxic treatment of H460 cells rendered cells 4-fold more susceptible to L-OddC but not to gemcitabine (dFdC) following exposure to drugs for one generation. Using hypoxia response element-luciferase reporter system, Western blotting, and immunohistochemistry, it was found that hypoxia-inducible factor-1α and PGK expression increased and could be correlated to tumor size. Despite dFdC being more toxic than L-OddC in cell culture, L-OddC (300 mg/kg i.p.) had a stronger antitumor activity than dFdC in H460 xenograft-bearing nude mice. Furthermore, L-OddC retained ~50% of its antitumor activity with oral gavage compared with i.p. delivery. Oral administration of L-OddC (600 mg/kg p.o.) had a similar area under the curve value compared with i.p. injection of dFdC (300 mg/kg i.p.). In conclusion, the hypoxia, which commonly exists in non-small cell lung carcinoma or other solid tumors resistant to radiotherapy or chemotherapy, is a favorable determinant to enhance the antitumor activity of L-OddC in vivo. [Mol Cancer Ther 2009;8(2):415–23]

Introduction
β-L-Dioxolane-cytidine (L-OddC; BCH-4556, troxacitabine) is a novel L-configuration deoxycytidine analogue with anticancer and antiviral (hepatitis B virus and HIV) activity (1–4). It was shown in clinical evaluations to be effective against both leukemias and solid tumors. Phase II clinical studies have shown that L-OddC has significant antileukemic activity in patients with acute myeloid leukemia and chronic myelogenous leukemia in the blastic phase (5) and modest activity in advanced pancreatic adenocarcinoma (6), renal cell carcinoma (7), and non-small cell lung carcinoma (8). It is currently under consideration for beginning phase I/II clinical trials for the treatment of solid tumors.

The metabolism of L-OddC is very different from D-configuration nucleoside analogues. Unlike many D-configuration nucleoside analogues, the cellular uptake of L-OddC is more dependent on passive diffusion than nucleoside transporter uptake (9). Tumor cells that are resistant to D-configuration nucleoside analogues due to underexpression of nucleoside transporters are sensitive to L-OddC (9). L-OddC is not catabolized by cytidine deaminase, which deaminates many D-configuration deoxyinosine nucleoside analogues, such as araC and gemcitabine (dFdC). Intracellularly, L-OddC is phosphorylated by deoxycytidine kinase (dCK) to its monophosphate metabolite that is further phosphorylated to the diphosphate and triphosphate metabolites by cellular kinases (2). The triphosphate metabolite of L-OddC can be incorporated into DNA in vitro by different DNA polymerases α, β, δ, γ, and ε (10). Because L-OddC lacks a hydroxyl group at the 3'-position, once incorporated into DNA, it causes premature termination of DNA replication and eventually leads to cell death. Therefore, the cytotoxicity of L-OddC is dependent on the steady-state level of the incorporated L-OddC in nuclear DNA. This level is affected by the amount of L-OddCTP formed by phosphoglycerate kinase (PGK; refs. 11–13) as well as the removal of L-OddCMP from the 3'-termini of DNA by apurinic/apyrimidinic endonuclease-1 (APE-1; refs. 14, 15).

In culture, the up-regulation of PGK by hypoxia-inducible factor (HIF)-1α under hypoxic conditions can make cells more susceptible to L-OddC (16). Hypoxic conditions, with oxygen partial pressures of 5 to 10 mm Hg: 0.7% to 1.4% oxygen in gas phase, are also commonly detected in solid tumors including lung cancer (7.5 mm Hg;
Effect of Hypoxia on the Cytotoxicity of L-OddC

Materials and Methods

Cell Culture

H460 (non-small cell lung carcinoma) cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum and 4.5 g/L glucose and 25 mmol/L HEPES (pH 7.4) in a 37°C humidified incubator with a 5% CO2 atmosphere or in a 37°C hypoxic chamber that was perfused with a gas mixture of 1% O2, 5% CO2, and 95% N2.

Western Blotting

Details of the Western blotting procedure are published in our previous report (16). Monoclonal anti-HIF-1α (1:2,000; BD Bioscience), monoclonal anti-PGK, or monoclonal anti-APE-1 (1:2,000; ref. 19) were used as an internal control to ensure equal protein loading and was detected with a monoclonal actin antibody diluted 1:2,500 (Sigma).

Confocal Microscopy

Details of the immunofluorescence staining procedure are published in our previous report (16). Monoclonal anti-HIF-1α, monoclonal anti-PGK, or monoclonal anti-APE-1 (1:3,000; Novus) was used to detect the corresponding proteins. Cytoplasmic actin was counterstained with a monoclonal actin antibody diluted 1:2,500 (Sigma). A 0.25 g/mL rhodamine phalloidin (Molecular Probes) was made and incubated with Hypoxyprobe 1MAb1 (IgG1), a monoclonal antibody that detects protein adducts of Hypoxyprobe in hypoxic cells and then subjected to streptavidin peroxidase/3,3′-diaminobenzidine tetrahydrochloride (DAB) development according to the Hypoxyprobe protocol.

Animal Studies

Male NCr-nude mice (average body weight of 20 g), age 4 weeks, were obtained from Taconic Farms and acclimated to laboratory conditions 1 week before tumor implantation. Nude mice were maintained in accordance with the Institutional Animal Care and Use Committee procedures and guidelines. Human H460 tumor xenografts were established by s.c. injection. L-OddC (gift of David C.K. Chu, Ph.D., University of Georgia School of Pharmacy) and dFdC were dissolved in PBS to 30 mg/mL. Both L-OddC and dFdC (Eli Lilly) were administered by i.p. injections.
(300 mg/kg), whereas L-OddC was also given by oral gavage (300 or 600 mg/kg). Tumor growth was measured daily using an electronic digital caliper (Fisher Scientific). Tumor volume was estimated by using the formula: \( \frac{\text{length} \times \text{width}^2 \times \pi}{6} \). Mice were weighed daily using a standard scale (Ohaus-Scout II) SC2020.

**Statistical Analysis**

Data were analyzed by two-way ANOVA (GraphPad Prism 4), Student’s \( t \) test (Microsoft Excel), and correlation analysis (GraphPad Prism 4). The difference was considered to be statistically significant when \( P < 0.05 \).

**Results**

**Antitumor Activity of L-OddC and dFdC In vivo**

As illustrated in Fig. 1A, we compared equivalent (300 mg/kg) dosages of L-OddC and dFdC on H460 tumor growth in NCR nude mice. During the first treatment (days 1-8), L-OddC (300 mg/kg i.p.) decreased the size of H460 tumor xenografts by 60\%, whereas dFdC (300 mg/kg i.p.) stabilized the H460 tumor xenografts until day 6 and the H460 tumor regrew at day 7 and 8. The second treatment of L-OddC (300 mg/kg i.p.) decreased the size of H460 tumor xenografts to almost immeasurable and the H460 tumor growth was repressed until day 20. The second treatment of dFdC (300 mg/kg i.p.) stopped the H460 tumor growth for 3 days and the H460 tumor rebound with a similar growth rate of control (Fig. 1A). In the two-cycle treatment protocol, L-OddC and dFdC delayed the H460 xenograft reaching 400\% initial tumor volume by 15 and 5 days, respectively (Fig. 1B). Our data clearly indicated that the antitumor activity of L-OddC is stronger than that of dFdC in a H460 xenograft tumor model in vivo. No weight loss was observed in either treatment group (data not shown).

Oral activity is one of the unique features of L-OddC, and dFdC is not orally active (3). Here, we examined whether L-OddC was orally active against H460 xenograft tumor

**Figure 1.** Anti-H460 xenograft tumor activity of L-OddC and dFdC in vivo. A, inhibition of H460 tumor growth by L-OddC (300 mg/kg i.p. or p.o. at days 1 and 9; arrow) and dFdC (300 mg/kg was delivered i.p. at days 1 and 9; arrow). B, time required for tumor to reach 400\% of initial tumor size after different treatments. C, comparison of the effect of i.p. and p.o. delivery of L-OddC on the inhibition of H460 tumor growth. Three experiments with five animals in each group were done and one of the representative experiments is presented.

**Figure 2.** Pharmacokinetics of L-OddC and dFdC in H460 xenograft tumor-bearing nude mice. A, mean \( \pm \) SD plasma concentration (\( n = 5 \)) versus time curves of L-OddC (300 mg/kg i.p. or 600 mg/kg p.o.) and dFdC (300 mg/kg i.p.). B, pharmacokinetic variables (area under the curve (AUC), \( C_{\text{max}} \), and \( t_{1/2} \)) of L-OddC and dFdC using i.p. or p.o. delivery.
in vivo. In the two-cycle treatment protocol, oral administration of l-OddC (300 mg/kg p.o.) showed a similar antitumor activity as dFdC (300 mg/kg i.p.) and ~50% antitumor activity compared with the i.p. delivery of l-OddC (300 mg/kg i.p.; Fig. 1A and B). In a single-dosage treatment protocol, the antitumor activity of oral administration of l-OddC with 600 mg/kg was similar to that of i.p. delivery of l-OddC with 300 mg/kg (Fig. 1C). There were no significant changes in animal weights during studies (data not shown).

Pharmacokinetics of l-OddC and dFdC in H460 Xenograft Tumor-Bearing Nude Mice

Comparison of the pharmacokinetics of l-OddC (300 mg/kg i.p.) and dFdC (300 mg/kg i.p.) was examined (Fig. 2A and B). l-OddC reached a maximum plasma concentration ($C_{\text{max}}$) of 1.2 mmol/L with an elimination half-life ($t_{1/2}$) of 21 min (Fig. 2A and B). The $C_{\text{max}}$ of dFdC was 0.62 mmol/L and the $t_{1/2}$ of dFdC was 17.5 min (Fig. 2A and B). Because l-OddC had a higher $C_{\text{max}}$ and longer $t_{1/2}$

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Figure 3. Transcriptional response of HRE in H460 cells in vitro and in vivo. A, luciferase reporter assay indicates the HRE of PGK promoter mediates transcriptional response to hypoxia. B, in vivo luciferase imaging shows that HIF-mediated transcriptional response was present in H460 tumor xenografts. C, pimonidazole was used as a hypoxia probe to detect the presence of hypoxic conditions in H460 tumor xenografts. The rest of the procedures was the same as described in Materials and Methods.
than that of dFdC, the area under the curve of L-OddC is 0.62 mmol h/L, which is 1-fold higher than that of dFdC.

Oral administration of L-OddC had a very different pharmacokinetic profile than i.p. delivery of L-OddC. Oral administration of L-OddC took 30 min to reach its $C_{max}$ of 0.22 mmol/L, and the $t_{1/2}$ after oral administration of L-OddC was 111 min, which is 5-fold longer than the $t_{1/2}$ for i.p. delivery of L-OddC. The relative bioavailability of L-OddC was 50% of the i.p. amount following oral administration (Fig. 2B). The area under the curve for L-OddC (600 mg/kg p.o.) was about the same as that of dFdC (300 mg/kg i.p.).

**Effect on Hematologic Function**

Data from our experiments support that the toxicities of L-OddC and dFdC are very similar in their suppression of select leukocyte populations when given at 300 mg/kg i.p. and measured on day 4 (Table 1). By day 16, drug-treated
groups leukocyte counts were at least equivalent to pretreatment levels. Control mice had a significant increase of their neutrophil counts from pretreatment levels ($P = 0.0064$) on day 16.

Platelet and erythrocyte counts were not significantly different from control on day 4. On day 16, L-OddC platelet levels were well within normal limits but statistically less than control ($P = 0.0198$) or dFdC ($P = 0.0013$). These data suggest a similar acute hematologic toxicologic profile of these compounds in nude mice.

Transcriptional Response of HRE of PGK Promoter in H460 Cells In vivo

In normoxic conditions, similar luciferase activity per cell was detected in H460 cells carrying mutated or wild-type HRE reporters (Fig. 3A). In hypoxic conditions, 10-fold higher luciferase activity per cell was found in H460 cells carrying wild-type HRE reporter than that with mutated HRE reporter (Fig. 3A). In similar-sized H460 tumor xenografts, H460 cells with HRE reporter had much higher luciferase activity than H460 cells with mutated HRE reporter (Fig. 3B). This showed that the HIF-mediated transcriptional response was present in H460 tumor xenografts. Furthermore, hypoxia (pimonidazole) staining clearly indicated that some areas of H460 xenograft tumors were lacking oxygen (Fig. 3C).

Protein Levels of HIF-1α, PGK, and APE-1 in H460 Tumor Sections

Because hypoxic conditions (oxygen partial pressure 5-10 mm Hg; 0.7-1.4% oxygen in gas phase) are commonly detected in solid tumors, and the induction of HIF-1α in hypoxic conditions can induce the expression of PGK, which can facilitate the synthesis of the triphosphate metabolite of L-OddC, we also studied the immunostaining of HIF-1α and PGK in H460 tumor xenografts from our nude mouse model. As shown in the micrographs, the HIF-1α-stained area increased with tumor progression (Fig. 4A). Most of the HIF-1α-stained cells were found between necrotic and intact cell populations. The intensity of PGK staining, but not APE-1 staining, increased as the tumor size increased. Western blot analysis indicated that the expression of HIF-1α and PGK, but not APE-1, had a positive correlation with the tumor size (Fig. 4B; Supplementary Fig. S1). Furthermore, PGK protein expression had a positive correlation to HIF-1α (Fig. 4B). The size of tumor had no significant effect on the expression of dCK, CMPK, and nM23 H1 in H460 tumor xenografts (Fig. 4B).

Figure 5. Protein expression of HIF-1α, HIF-1β, PGK, APE-1, CMPK, nM23 H1, and dCK of H460 cells in the hypoxic conditions (1% O₂, 5% CO₂, and 94% N₂). A, Western blotting for the protein expression of HIF-1α, HIF-1β, PGK, APE-1, CMPK, nM23 H1, and dCK of H460 cells after exposing to hypoxic conditions for 24 h ($\beta$-actin staining was used for normalizing total protein loading). B, Immunofluorescence micrographs for determination of the subcellular localization of the induced HIF-1α, PGK, and APE-1 of H460 cells after 24 h hypoxic treatment.
Effects of Hypoxia on the Protein Expression on PGK, APE-1, dCK, CMPK, and nM23 H1

The induction of HIF(s) (heterodimer; HIF-1α/β) activates its downstream target genes through its interaction with the HRE (acgtg or gcgtg) of the promoter of the target genes in hypoxic conditions, and this interaction will result in the alteration of gene expression of many proteins, including PGK. As shown in Fig. 5A, the basal level of HIF-1α in H460 cells was very low in normoxic conditions, but HIF-1α was induced after 24 h of hypoxic treatment. The protein level of HIF-1β was not affected by hypoxia treatment. Immunofluorescence micrographs showed that the induced HIF-1α was translocated into the nuclei of H460 cells (Fig. 5B).

The effect of hypoxia on PGK, which is responsible for L-OddCTP formation, and APE-1, which has exonuclease activity that can remove the incorporated L-OddCMP from the 3'-DNA terminus and cause L-OddC resistance in cell culture, was determined with Western blotting. Results showed that 24 h of hypoxia treatment increased the protein level of PGK in H460 cells by ~3-fold (Fig. 5A). The protein level of APE-1 was not affected by hypoxia treatment (Fig. 5A). Immunofluorescent micrographs showed that hypoxia had no effect on the subcellular distributions of the PGK protein, which was present mostly in cytoplasm, and the APE-1 protein, which was present in the nuclei of H460 cells (Fig. 5B).

Besides the PGK protein, we also examined the effect of hypoxia on several key enzymes, dCK (L-OddC and dFdC to L-OddCMP and dFdCMP), CMPK (L-OddCMP and dFdCMP to L-OddCDP and dFdCDP), and nM23 H1 (dFdCDP to dFdCTP), responsible for different phosphorylation steps of L-OddC and dFdC. Hypoxia, however, had no effect on the level of these proteins in H460 cells (Fig. 5A).

Effect of Hypoxia on the Cytotoxicity and the Metabolism of L-OddC and dFdC in H460 Cells

In cell culture, dFdC is more toxic than L-OddC in H460 cells. Taking into consideration the 50% reduced growth rate under hypoxic conditions, clonogenic assay results indicated that hypoxia treatment could sensitize H460 cells by ~4-fold to L-OddC on the same generation time with exposure to the drug (Fig. 6A). The above result could be attributed to the increase of the triphosphate level and the DNA incorporation of L-OddC in hypoxic conditions (Fig. 6C and E; Supplementary Fig. S2). However, hypoxic treatment did not significantly sensitize H460 cells to dFdC on the same generation time exposure of the drug (Fig. 6B). Indeed, the triphosphate level of dFdC was not affected by hypoxic treatment (Fig. 6D). DNA

![Figure 6. Effect of hypoxic conditions on the cytotoxicity and the metabolism of L-OddC and dFdC in H460 cells. Cytotoxicity (A and B) of L-OddC and dFdC of H460 cells under normoxic conditions and hypoxic conditions. ID50 was defined as the concentration of drug required to achieve 50% of surviving fraction. Mean ± SD of three experiments, with each data point done in triplicate. Triphosphate level (C and D) and DNA incorporation (E and F) of L-OddC and dFdC of H460 cells in the normoxic and hypoxic conditions. The other phosphorylated forms of L-OddC and dFdC were shown in Supplementary Fig. S2.](http://www.mct.aacrjournals.org/content/8/2/421)
incorporation of dFdC was decreased in hypoxic conditions (Fig. 6F), and this could be the result of a reduction of DNA synthesis in H460 cells after hypoxic treatment (Supplementary Fig. S3).1

Discussion
The efficacy of l-OddC against solid tumors has been shown in many tumor models including prostate, renal, colon, head and neck, non-small cell lung, hepatocellular, and pancreatic cancer in vivo (2–4). In cell culture studies, dFdC often has a stronger cytotoxicity compared with l-OddC. However, in vivo, l-OddC had been reported to have a stronger antitumor activity than dFdC in several tumor models including Panc-1 (confirmed by us and data not shown; ref. 20), MiaPaCa model (dFdC refractory), and AsPC-1 (22). Here, we also showed l-OddC had a stronger inhibitory effect, than dFdC, on the growth of H460 tumor xenografts in a nude mouse model.

Pharmacokinetic analysis indicated that l-OddC had a higher Cmax and longer t1/2 than that of dFdC using i.p. delivery. The shorter t1/2 of dFdC could be caused by cytidine deamination, which eliminates many n-configura-
tion nucleoside analogues including dFdC but not l-OddC. Because the area under the curve of l-OddC was 1-fold higher than that of dFdC, this could be one of the reasons why l-OddC has a stronger inhibitory effect on H460 tumor xenografts than dFdC.

It has been reported that l-OddC is an orally active compound (3). Here, our results showed that l-OddC retained ~50% of its antitumor activity with oral gavage compared with i.p. delivery. Similar area under the curve values were found from oral administration of l-OddC (600 mg/kg p.o.) and i.p. injection of dFdC (300 mg/kg i.p.), l-OddC (300 mg/kg p.o.) treatments had stronger antitumor activity than dFdC (300 mg/kg i.p.). These results are unexpected because the ID50 of dFdC is 200-fold lower than that of l-OddC in H460 cells under normoxic culture conditions. Some factors, which possibly potentiate the action of l-OddC and/or suppress the action of dFdC, should be present in solid tumors. Studies have shown that most solid tumors have areas of hypoxia due to the abnormal development of the vascular system leading to decreased blood perfusion. We reported previously that hypoxia could induce PGK expression in different cell types and that hypoxia treatment made cells more susceptible to l-OddC but not to dFdC in culture (16). The possible reason is that induction of PGK under hypoxia can facilitate the synthesis of l-OddCCTP and result in an increase of l-OddC incorporation into DNA.

Here, we examined if hypoxic conditions can sensitize H460 cells to l-OddC in culture and if hypoxic conditions could be detected in H460 xenograft tumors. In culture, hypoxic treatment induced the protein expression of PGK by 3-fold but had no effect on the protein expression of APE-1, dCK, CMPK, and nM23 H1. As a result, the triphosphate level and DNA incorporation of l-OddC increased in hypoxic conditions. Using a clonogenic assay, hypoxic treatment of H460 cells made them 4-fold more susceptible to l-OddC but not to dFdC following exposure to drugs for one generation (Fig. 6B). Hypoxic conditions in the H460 tumor model was detected using a hypoxic probe: pimonidazole (Fig. 3C). Demonstration that a HIF-1α-mediated transcriptional response did occur in H460 tumor model using an in vivo luciferase imaging was also made. It is interesting that the expression of HIF-1α and PGK, but not other proteins involved in the metabolism of l-OddC, has a positive correlation with the tumor size. It is well known that hypoxic conditions induce HIFs, which turn on transcriptional programs that can result in more aggressive and metastatic cancer phenotypes, and are associated with resistance to radiation therapy, chemotherapy, and poor treatment outcomes. However, our results imply that hypoxic conditions in solid tumors will induce PGK expression, which can facilitate the conversion of l-OddC into its active metabolite. Because the size of solid tumors has a good correlation with the expression of HIF-1α and PGK, this suggests that l-OddC may maintain activity in larger, late-stage solid tumors.

Clinical studies have indicated that l-OddC possesses antitumor activity toward different kinds of tumors including leukemia and solid tumors. Extensive clinical trials have shown l-OddC to have a relatively strong antileukemic activity (23, 24). The exploration of the anti-solid tumor activity of l-OddC is limited, but the results are encouraging. First, in a phase II clinical trial for pancreatic cancer with a protocol 1.5 mg/m2 × 5 days, i.v. 30 min × 4 weeks, best responses were stable disease in 24 patients with 8 patients having stable disease for at least 6 months (15%) and 3 patients have stable disease for >1 year (6). One-year and overall survival from the above trial is comparable with those reported with single-agent dFdC. The activity of l-OddC in pancreatic adenocarcinoma was also evidenced by the observation that 16% of patients had a ≥50% decrease in CA 19-9 levels (a cancer marker of the pancreas and bile ducts), a result comparable with that achieved with dFdC. Secondly, an i.v. infusion of l-OddC (10 mg/m2), given over 30 min, had modest efficacy in 35 advanced renal cell carcinoma cases. Of the 33 patients, 2 patients were confirmed partial responses, 21 (60%) patients had stable disease (median duration, 4.4 months), and 10 patients had progressive disease (7). Eight patients remained stable for >6 months, of whom 6 remain free of progression. Because ~45% of renal cell carcinomas have defects in the von Hippel-Lindau gene, which plays a key role in degrading HIF-1α under normoxic conditions, HIF-1α and its downstream proteins (PGK, etc.) are likely to be overexpressed (25). Because of this, von Hippel-Lindau minus renal cell carcinoma subpopulations receiving l-OddC may have increased drug activity compared with the von Hippel-Lindau-positive population. Third, l-OddC was also administered to 17 patients with non-small cell lung carcinoma in a phase II trial. After receiving l-OddC as an i.v. infusion (10 mg/m2 over 30 min on day 1 every 21 days), 8 (47%) patients achieved stable disease with a median duration of 3.6 months (range, 2.0–7.1; ref. 8).
In conclusion, the hypoxic condition present in solid tumors, which increase radiation and chemotherapy resistance, seems to be a favorable factor for the activity of L-OddC. The evaluation of L-OddC anti-solid tumor should be further explored.

Disclosure of Potential Conflicts of Interest

Y-C. Cheng, co-inventor of L-OddC with potential financial interest in the compound. No other potential conflicts of interest were disclosed.

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