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A solid lipid nanoparticle formulation of 4-(*N*)-docosahexaenoyl 2′, 2′-difluorodeoxycytidine with increased solubility, stability, and antitumor activity

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ABSTRACT

Previously, we synthesized 4-(*N*)-docosahexaenoyl 2′, 2′-difluorodeoxycytidine (DHA-dFdC), a novel lipophilic compound with a potent, broad-spectrum antitumor activity. Herein, we report a solid lipid nanoparticle (SLN) formulation of DHA-dFdC with improved apparent aqueous solubility, chemical stability, as well as efficacy in a mouse model. The SLNs were prepared from lecithin/glycerol monostearate-in-water emulsions emulsified with D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) and Tween 20. The resultant DHA-dFdC-SLNs were 102.2 ± 7.3 nm in diameter and increased the apparent solubility of DHA-dFdC in water to at least 5.2 mg/mL, more than 200-fold higher than its intrinsic water solubility. DHA-dFdC in a lyophilized powder of DHA-dFdC-SLNs was significantly more stable than the waxy solid of pure DHA-dFdC. DHA-dFdC-SLNs also showed an increased cytotoxicity against certain tumor cells than DHA-dFdC. The plasma concentration of DHA-dFdC in mice intravenously injected with DHA-dFdC-SLNs in dispersion followed a bi-exponential model, with a half-life of ~44 h. In mice bearing B16-F10 murine melanoma, DHA-dFdC-SLNs were significantly more effective than DHA-dFdC in controlling the tumor growth. In addition, histology evaluation revealed a high level of apoptosis and tumor encapsulation in tumors in mice treated with DHA-dFdC-SLNs. DHA-dFdC-SLNs represents a new DHA-dFdC formulation with improved antitumor activity.

1. Introduction

Previously we synthesized DHA-dFdC (Fig. 1A) by conjugating docosahexaenoic acid (DHA), a omega-3 polyunsaturated fatty acid (PUFA), to gemcitabine (2′, 2-difluorodeoxycytidine, dFdC) on its 4-N position (Naguib et al., 2016). DHA-dFdC showed potent and broad-spectrum antitumor activity against the National Cancer Institute (NCI)-60 human tumor cell lines and was significantly more effective than the molar equivalent dose of gemcitabine in controlling tumor growth in several mouse models of pancreatic cancer, including a genetically engineered mouse model and athymic mice with orthotopically transplanted human pancreatic tumor cells (Naguib et al., 2016). However, DHA-dFdC is poorly soluble in water (i.e. intrinsic solubility, ~25 μg/mL), and a formulation in which DHA-dFdC is chemically more stable than in the current Tween 80-ethanol-in-water formulation is desired (Naguib et al., 2016).

SLNs have emerged as an attractive delivery system for poorly water-soluble drugs (Feng and Mumper, 2013; Geszke-Moritz and Moritz, 2016; MuÈller et al., 2000). There is also evidence that incorporation of a drug into SLNs can increase its chemical stability (Lim et al., 2004; Patel et al., 2012; Üner et al., 2005). Previously, our group developed an SLN formulation based on a lecithin/glycerol

Abbreviations: DHA-dFdC, 4-(*N*)-docosahexaenoyl 2′, 2′-difluorodeoxycytidine; DHA, docosahexaenoic acid; DMSO, dimethyl sulfoxide; DMEM, Dulbecco's Modified Eagle Media; dFdC, 2, 2,-difluorodeoxycytidine; FBS, fetal bovine serum; GPC, gel permeation chromatography; HPLC, High-performance liquid chromatography; i.v., intravenous; Kcps, kilo counts per second; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide); NMR, nuclear magnetic resonance; PEG, polyethylene glycol; PK, pharmacokinetic; PBS, phosphate-buffered saline; PUFA, polyunsaturated fatty acid; rcf, relative centrifugal force; SLNs, solid lipid nanoparticles; TEM, transmission electron microscopy; THF, tetrahydrofuran; TPGS, D-α-tocopherol polyethylene glycol 1000 succinate; GMS, glycerol monostearate; s.c., subcutaneous

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