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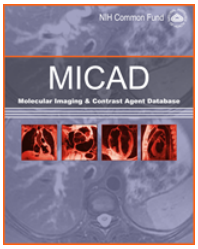

Doxorubicin-loaded poly(ethylene oxide)-trimellitic anhydride chloride-folate superparamagnetic iron oxide nanoparticles

YCC-DOX

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Chemical name:	Doxorubicin-loaded poly(ethylene oxide)-trimellitic anhydride chloride-folate superparamagnetic iron oxide nanoparticles	
Abbreviated name:	YCC-DOX	
Synonym:		
Agent Category:	Nanoparticles	
Target:	Folate receptor (FR)	
Target Category:	Receptor	
Method of detection:	Magnetic resonance imaging	
Source of signal / contrast:	Superparamagnetic iron oxide	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals	Structure not available in PubChem.

Background

[PubMed]

Because of low specificity, many cancer therapeutic agents (most small molecules and some targeted biopharmaceuticals) used to treat malignancies often have severe systemic toxicity and other undesirable side effects in a patient (1, 2). Therefore, to reduce the toxicity and side effects of an anticancer drug, either the chemical structure of the compound has to be altered or a drug delivery system must be used to specifically target the drug to affected organs or tissues such that the surrounding normal tissues are not affected by the antineoplastic agent. Investigators have developed and evaluated various nanocarrier drug delivery systems, including nanoparticles (NPs), to target and deliver drugs for the detection, treatment, and imaging of diseased tissues and organs up to the cellular level (3). Doxorubicin (DOX) is an anthracycline-based antibiotic that is used as an antineoplastic agent against several different cancers types, but its application in the clinic is limited by the dose-dependent cardiotoxicity and cytotoxicity observed in many patients (4). As a consequence, a

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pegylated liposomal NP preparation of DOX (PLD) was developed and shown to have a long blood circulation half-life (2–3 days *versus* 5 min for free DOX) and had a very high accumulation in tumors compared to the normal surrounding tissue. In addition, PLD alone had a superior treatment outcome (in comparison to DOX used at the same concentration in combination with two other chemotherapeutic agents) and showed lower toxicity (5). Anticancer drugs have also been encapsulated in different types of NPs, such as superparamagnetic iron oxide (SPIO) NPs, that are conjugated to target-seeking molecules, bind only to cells that produce the appropriate biomarker, are used as magnetic resonance imaging (MRI) contrast agents, and serve as multifunctional drug delivery and imaging agents (6). The structure, biological characteristics, and therapeutic and imaging applications of SPIOs are described elsewhere (7).

Maeng et al. synthesized a polymeric NP that contained DOX and an SPIO and evaluated the efficacy of the NPs, designated YCC-DOX, as a targeted therapeutic agent against hepatic cancer and as an MRI agent in rats and rabbits having liver cancer lesions induced by diethylnitrosamine (DEN; has carcinogenic and mutagenic properties) and O-ethyl O-2-diisopropylaminoethyl methylphosphonite (VX2; a nerve agent), respectively (8). The NP contained poly(ethylene oxide)-trimellitic anhydride chloride-folate, where the folate component serves as the tumor-targeting molecule because it has a very high affinity (K_d, ~10^{-10} M) for the folate receptor (FR). Also, the FR is overexpressed in many human cancers, and the FR-folate structure is rapidly internalized by the cell through endocytosis, resulting in targeted delivery of the drug to the tumor cells (8).

Other Sources of Information Related to Folate Receptor

Adult human FR protein and mRNA sequences.

Human FR gene. (Gene ID: 2348)

FR Clinical trials.

FR in Online Mendelian Inheritance in Man (OMIM) database.

FR pathway in Kyoto Encyclopedia of Genes and Genomes (KEGG).

Synthesis

[PubMed]

The synthesis of folate containing YCC-DOX has been described by Maeng et al. (8). The net yield of the NP after synthesis was reported to be 85–94 mol percent based on the amount of folic acid incorporated (8). The NPs were determined to contain 2.1 mg/mL DOX and 2.5 mg/mL iron. The average diameter of the YCC-DOX NP was 84.7 nm as determined with a submicron particle size analyzer and transmission electron microscopy revealed that the particles had a spherical shape.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The release of DOX from YCC-DOX was investigated under *in vitro* conditions as described by Maeng et al. (8). At pH 5.1 and 7.4, approximately 56% and 33% DOX, respectively, was released from the NPs within 24 h, indicating that the NPs were relatively stable at a physiological pH. This study indicated that the rate of DOX release from the NPs was almost two-fold higher at the acidic pH (e.g., as found in the endosomes and the lysosomes of tumor cells) than at physiological pH.

For competitive inhibition studies, the cellular uptake of YCC-DOX was studied by separately exposing Hep3B (a human hepatocellular carcinoma cell line that overexpresses the FR) and KB cells to YCC-DOX NPs with or

without FA pretreatment (2 mM) for competitive inhibition (8). The uptake of YCC-DOX NPs was visualized with a confocal laser scanning microscope, and both cell types pretreated with DOX were shown to have a reduced uptake of the NPs compared to the untreated cells.

The cytotoxicity of YYC-DOX NPs was compared to that of free DOX (FD) and a commercially available liposomal preparation of DOX (CD) using Hep3B cells (8). The cells were exposed to the different preparations of DOX, and cell viability was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (also known as the MTT assay) at 24 h and 48 h after exposure to DOX. At both time points, YCC-DOX NPs were shown to reduce the cell viability from 100% to ~50% and ~20% at 24 h and 48 h, respectively, at a concentration of 100 μM DOX, similar to results with FD. However, with CD the cell viability remained >80% at these time points at the same concentration of DOX.

In another *in vitro* study, the MRI signals of YCC and YCC-DOX (at iron concentrations of 0–25 μg/mL) from T2-weighted images acquired at a 1.5-T, fast spin echo, with a TR ¼ 3,600 ms and TE ¼ 88.6 ms, were shown to be higher than a commercially available liver-specific MRI contrast agent at the same iron concentrations (8).

Animal Studies

Rodents

[PubMed]

DEN-Treated rats with hepatic cancer were divided into four drug treatment groups as follows: saline-treated (n = 6 animals; this was the control group), FD-treated (n = 10 animals), CD-treated (n = 10 animals), and YCC-DOX–treated (n = 10 animals) (8). The animals in each group were intravenously injected through the tail vein with the respective drug preparations (2 mg DOX equivalent/kg body weight) three times at 5-day intervals (days 0, 5, and 10). The tumor volumes, the relative volumes, signal intensity (using MRI), and normalized signal intensity of animals in the different groups were measured or calculated on day 0 and day 20 as described by Maeng et al. (8). In the YCC-DOX–treated animals, the relative volumes of the tumors were reported to decrease by 19.3-, 3.5-, and 4.5-fold compared to the rats treated with saline, FD ($P < 0.05$), and CD ($P < 0.002$), respectively. No blocking studies were reported.

In another experiment, MRI was performed on rats with DEN-induced hepatic tumors (number of animals not specified) and intravenously injected with the same volume of either YCC, YCC-DOX (each containing 2.5 mg iron/mL), or contrast agent (containing 27.9 mg iron/mL). T2- or T2*-Weighted images were acquired using either a 1.5-T, fast spin echo, with a TR and TE of ¼ 3,600 ms and ¼ 83.5 ms, respectively, or a 1.5-T, gradient-recalled echo, with a TR and TE of ¼ 30 ms and ¼ 13.9 ms, respectively. The animals were imaged before and after an intravenous injection of the agents and a decrease in the tumor signal intensity of the YCC-DOX–treated rats was noted to be significantly higher (P value not provided) than the contrast agent–treated animals as determined from the T2-weighted images. In addition, the signal intensities obtained from the YCC- and the YCC-DOX–treated animals were reduced by ~40% compared to the other treatments. No blocking studies were reported.

Other Non-Primate Mammals

[PubMed]

In a study similar to that performed with the rats (see above), rabbits (n = 6–10 animals/group) bearing VX2-induced hepatic tumors were treated with the various preparations of DOX as listed above, including a saline-treated control group (8). Subsequently, relative volume values were obtained from the rabbits as detailed above, and it was shown that the values decreased 21.5-, 2.4- and 3.5-fold in the YYC-DOX–treated animals compared to animals in the saline-, FD-, and CD-treated groups, respectively. This indicated that the effect of the YCC-

DOX preparation in rabbits bearing the VX2-induced tumors was similar to that observed with rats bearing the DEN-induced hepatic tumors. No blocking studies were reported.

The YCC-DOX–treated rabbits showed little cardiac toxicity, oral mucositis, or hair loss compared to the animals treated with FD and CD (8). The mortality rate of animals treated with the FD and CD preparation was nearly 10% and 33%, respectively, compared with 0% for the YCC-DOX–treated rabbits.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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