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Improving nucleoside analogs *via* lipid conjugation: Is fatter any better?

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ABSTRACT

In the past few decades, nucleoside analog drugs have been used to treat a large variety of cancers. These anti-metabolite drugs mimic nucleosides and interfere with chain lengthening upon incorporation into the DNA or RNA of actively replicating cells. However, efficient delivery of these drugs is limited due to their pharmacokinetic properties, and tumors often develop drug resistance. In addition, nucleoside analogs are generally hydrophilic, resulting in poor bioavailability and impaired blood-brain barrier penetration. Conjugating these drugs to lipids modifies their pharmacokinetic properties and may improve *in vivo* efficacy. This review will cover recent advances in the field of conjugation of phospholipids to nucleoside analogs. This includes conjugation of myristic acid, 12-thioethyldodecanoic acid, 5-elaidic acid esters, phosphoramidate, and self-emulsifying formulations. Relevant *in vitro* and *in vivo* data will be discussed for each drug, as well as any available data from clinical trials.

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1. Introduction

Nucleoside analogs are a class of synthetic cytotoxic antimetabolite drugs commonly used as primary treatment for a variety of cancers, particularly hematologic malignancies (Fig. 1). These drugs closely resemble endogenous purine and pyrimidine nucleosides, and their primary mechanism of action is chain termination upon incorporation into nucleic acid strands *via* inhibition of DNA or RNA polymeraes.

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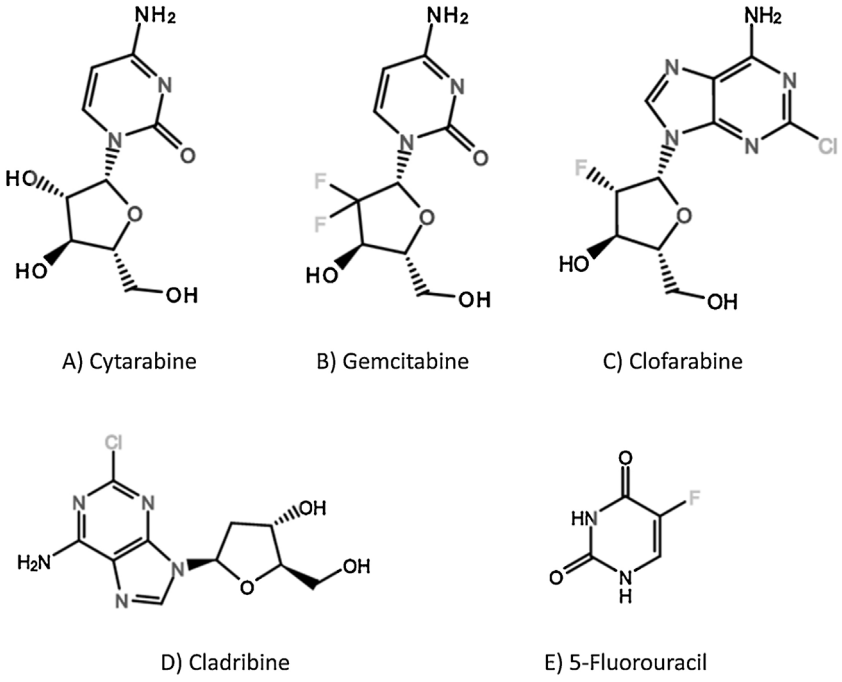

Fig. 1. Chemical structures of conventional nucleoside analogs (A) cytarabine (B) gemcitabine (C) clofarabine (D) cladribine, and (E) 5-fluorouracil.

Nucleoside analogs require transport by the human equilibrative nucleoside transporter 1 (hENT1) to enter cells (Galmarini et al., 2002). Once inside the cell, phosphorylation to the monophosphate form of the drug is mediated by cellular kinases, which is often the rate-limiting step of activation (Staub and Eriksson, 2007). Two further phosphorylation steps are required to produce the active triphosphate form, which can then be incorporated into growing nucleic acid chains. Once incorporated, these drugs cause DNA chain termination and DNA strand breaks, leading to apoptosis (Genini et al., 2000). The nucleoside analogs, gemcitabine and clofarabine, also can inhibit ribonucleotide reductase (Baker et al., 1991; Aye et al., 2012), and two others, decitabine and azacytidine, can inhibit DNA methyltransferases (Beumer et al., 2008). The activity of these drugs depends on their incorporation into replicating DNA during S phase of the cell cycle and is not specific to cancer cells; rapidly dividing normal cells (including those in the bone marrow, gastrointestinal tract, and hair follicles) are often damaged as well. This results in the unwanted side effects that limit clinical administration of nucleoside analogs including myelosuppression, mucositis, and hair loss.

Many patients develop resistance to nucleoside analog agents, ultimately reducing their clinical benefit. Resistance mechanisms include reduced drug uptake due to decreased expression of transport proteins such as hENT1, increased activity of the *P*-glycoprotein drug efflux pump, lower rates of drug activation due to loss of deoxycytidine kinase (dCK) expression, and inactivation due to deamination by cytidine deaminase for Ara-C and gemcitabine or ribonucleotide reductase and nuclear exonucleases for fludarabine (Peters et al., 1993). Conventional nucleoside analogs exhibit poor passive diffusion across the gastrointestinal tract and require active transport by either concentrative or equilibrative transporters (Balimane and Sinko, 1999). All these factors limit oral bioavailability of these drugs, so they must be given intravenously (Galmarini et al., 2002). The short comings of current nucleoside analogs are summarized in Fig. 2. Researchers began modifying nucleoside analogs shortly after they were first approved for clinical use. The development of novel pro-drugs or conjugates by attaching various lipid moieties to the parental drugs has improved their pharmacokinetic properties, including uptake, plasma half-life, and activity *in vivo*. This review will focus on recent advances in nucleoside analogs conjugated to phospholipid groups, fatty acids or packaged in liposomes.

2. Lipid-drug conjugate chemistry

Most lipid-drug conjugate chemistry utilizes liposomal incorporation, salt formation with a fatty acid, or covalent linkage of esters, ethers, glycerides, or phospholipids to create novel pro-drugs (Allen and Cullis, 2004; Yatvin et al., 1992; Lambert, 2000). Fatty acid con-

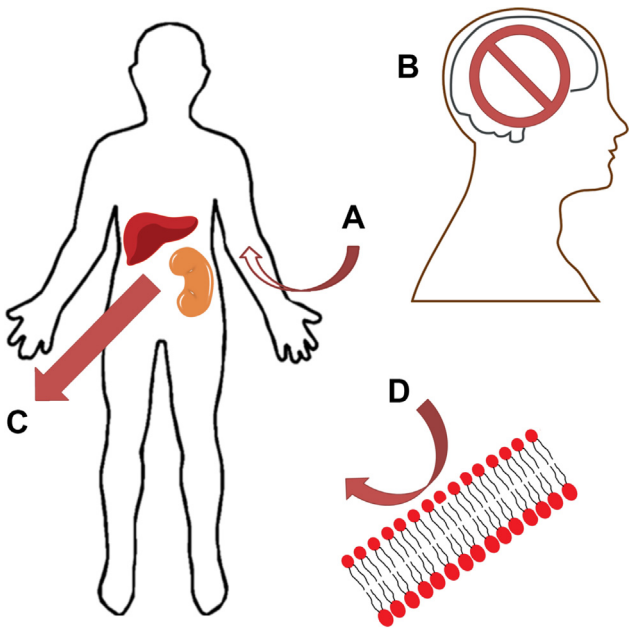

Fig. 2. Graphical depiction of the common short comings of nucleoside analogs. (A) Inconvenient administration (B) minimal blood brain barrier penetration at standard doses (C) rapid elimination and short half-life (D) do not penetrate the tumor cell membrane.

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