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Monitoring fluoropyrimidine metabolism in solid tumors with in vivo ^{19}F magnetic resonance spectroscopy

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Abbreviations: ACC, advanced colorectal cancer; ADEPT, antibody-directed enzyme-prodrug therapy; BAU, 5-benzylacyclouridine; B_0, static magnetic field; B_{eff}, effective magnetic field; CNDP, 3-cyano-2,6-dihydroxypyridine; 5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; DHFU, 5,6-dihydro-5-fluorouracil; DPD, dihydropyrimidine dehydrogenase; dTDP, 2′-deoxythymidine-5′-diphosphate; dTMP, 2′-deoxythymidine-5′-monophosphate; dTTP, 2′-deoxythymidine-5′-triphosphate; dUMP, 2′-deoxyuridine-5′-monophosphate; EM-FU, 1-ethoxymethyl-5-fluorouracil; EU, 5-ethynyluracil, eniluracil; F^-, fluoride; FAC, fluoroacetate; FBAL, α-fluoro-β-alanine; FCyt, 5-fluorocytosine; FdUDP, 5-fluoro-2′-deoxyuridine-5′-diphosphate; FdUMP, 5-fluoro-2′-deoxyuridine-5′-monophosphate; FdUrd, 5-fluoro-2′-deoxyuridine; FdUTP, 5-fluoro-2′-deoxyuridine-5′-triphosphate; FHPA, α-fluoro-β-hydroxypropionate; FID, free induction decay; ^{19}F MRS, fluorine-19 magnetic resonance spectroscopy; Fnucs, fluoronucleosides; Fnuct, fluoronucleotides; FU, 5-fluorouracil; FUDP, 5-fluorouridine-5′-diphosphate; FUMP, 5-fluorouridine-5′-monophosphate; FUPA, α-fluoro-β-ureidopropionic acid; FUrd, 5-fluorouridine; FUTP, 5-fluorouridine-5′-triphosphate; γ, magnetogyric ratio; GDEPT, gene-dependent enzyme prodrug therapy; HCFU, 1-hexylcarbamoyl-5-fluorouracil; IFNα, interferon-alpha; i.p., intraperitoneal; i.v., intravenous; L6-CD, L6 cytosine deaminase; LV, leucovorin; M, vector of magnetization; MRSI, magnetic resonance spectroscopic imaging; MTX, methotrexate; OPRTase, orotic acid phosphoribosyltransferase; ^{31}P, phosphorous-31; PET, positron-emission tomography; ppm, parts per million; PRPP, 5-phosphoribosyl-1-pyrophosphate; RF, radiofrequency; σ, shielding constant; SNR, signal-to-noise-ratio; Thd, thymidine; UFT, uracil and ftorafur; UrdPase, uridine phosphorylase; T, Tesla; T_1, longitudinal spin–lattice relaxation time; T_2, transverse, spin–spin relaxation time; TAPET-CD, attenuated *Salmonella typhimurium* strain recombinant to provide cytosine deaminase; TK, thymidine kinase; TMTX, trimetrexate; TP, thymidine phosphorylase; TS, thymidylate synthase; ω, Larmor frequency or MR frequency

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Abstract

^{19}Fluorine magnetic resonance spectroscopy (^{19}F MRS) offers unique possibilities for monitoring the pharmacokinetics of fluoropyrimidines in vivo in tumors and normal tissue in a non-invasive way, both in animals and in patients. This method may therefore be useful for predicting response to fluoropyrimidine-based therapy with or without the effects of modulating agents, and this may be of value for the individualization of anticancer therapy and the strategic development of new anticancer drugs. ^{19}F MRS has been very valuable in elucidating the basic aspects of fluoropyrimidine metabolism, especially in animal studies. Studies in humans have indicated its clinical potential, but widespread application has been hampered by the relatively low detection sensitivity of the method. The recent introduction of clinical MR scanners with magnetic fields above 1.5 T may stimulate increased clinical use of ^{19}F MRS.

Keywords: 5-Fluorouracil; Capecitabine; Tegafur; NMR; Spectroscopy; ^{19}F; Review

1. Introduction

In the past decades increasing numbers of chemotherapeutic agents have become available for cancer treatment. However, chemotherapy is often effective in only a subgroup of patients. A method for predicting the sensitivity of a tumor to chemotherapy would enable individualized therapy and minimization of systemic toxicity in non-responding patients. Parameters by which (non)response can be determined in an early stage are not only of interest for individual patients but also for drug development strategy. The initial extra effort in establishing patient selection criteria may far outweigh the costs of taking a drug through phase II and III trials in an unselected patient population.

The response of a tumor to chemotherapy depends not only on the intrinsic sensitivity of the tumor to a specific drug but also on the achieved concentration of the drug in the tumor, which in turn depends on influx of the drug into the tumor, intracellular uptake, metabolic activation and catabolism, and clearance of the drug from (tumor) tissue and the vasculature. Plasma levels of a drug or its metabolites may not correlate well with clinical response [1], since active metabolites may be trapped within the cell [2]. Magnetic resonance spectroscopy (MRS) is a non-invasive technique that can, in principle, be applied in vivo to determine the concentration of drugs in tumor tissue and to monitor the conversion of the parent drug to active metabolites and/or inactive catabolites. The drug 5-fluorouracil (FU), a fluoropyrimidine used in many chemotherapy regimens, can be monitored by fluorine-19 (^{19}F) MRS. Several reviews have been published concerning ^{19}F MRS of fluoropyrimidines [3–7]. However, since the publication of the most recent review in 2000 [7], several new in vivo preclinical and clinical ^{19}F MRS studies have emerged. Here, we review the major in vivo ^{19}F MRS studies dealing with FU and other fluoropyrimidines in rodents and patients, including the new studies, and discuss their impact on our understanding of fluoropyrimidine pharmacokinetics, metabolism and therapy outcome. The basic principles of fluoropyrimidine metabolism and MRS are presented as background material prior to the discussion of ^{19}F MRS of fluoropyrimidines in solid tumors.

2. Fluoropyrimidine metabolism

Because of the limited efficacy of FU as a single agent for tumor treatment, various attempts have been made to improve the results of FU treatment by modulating the uptake and/or metabolism of FU. More recently, fluoropyrimidines other than FU have been developed which may have the advantage of easier scheduling, simplified administration or a more favorable toxicity profile. Therefore, in the following we will summarize the metabolism of FU, methods of its modulation, and the most important fluoropyrimidines other than FU (see also reference [8]).

2.1. 5-Fluorouracil

Although many new drugs have been developed since the introduction of FU by Heidelberger et al. [9], it still remains one of the most important drugs in the treatment of colorectal cancer [8]. Combined with other drugs, it is also commonly employed for the treatment of other types of gastrointestinal cancers, breast cancer and head and neck cancer. FU is rapidly extracted from the circulation (ca. 85% during each passage) and metabolized in the liver [10]. In advanced colorectal cancer improved efficacy and tolerability for FU have