Abstract

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Thymidylate synthase inhibition in colorectal liver metastases can be improved with Arfolitixorin compared to Leucovorin.

The Modelle-001 Trial:
A Single-blinded, Randomised Phase II study investigating the effects of two doses of Arfolitixorin compared to Calcium folinate together with 5-fluorouracil on thymidylate synthase in tumour and adjacent hepatic tissue for patients with liver metastases from colorectal cancer.

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Background: The chemotherapeutic drug 5-fluorouracil (5-FU) is one of the cornerstones in treatment of colorectal cancer, by targeting the vital enzyme thymidylate synthase (TS). The cytotoxicity of the treatment results from inhibition of TS activity by the 5-FU metabolite FdUMP which forms a stable ternary complex with TS. The effect of 5-FU can be enhanced by reduced folates, most often racemic leucovorin (LV), that strengthens the complex. Polyglutamed folates are better stabilizers of the ternary complex than monoglutamated forms. In contrast to LV, arfolitixorin ([6R]5,10-methylenetetrahydrofolate) (Arfo) does not require enzymatic metabolic activation because it constitutes the active folate of the ternary complex. A hypothesis is therefore that patients who are uncapable of metabolizing LV could benefit from Arfo administration.

Aim: The Modelle-001 trial was designed to explore how a single intravenous bolus injection of Arfo as compared to LV in the form of calcium folinate, together with 5-FU affects the inhibition of TS and, further, to investigate how different forms and doses of folates affect folate concentration and polyglutamation in metastatic liver tissue.

Patients and Methods: Thirty adult patients with biopsy-verified colorectal cancer and liver metastases indicated for surgical removal were included at two Swedish University Hospitals. Both synchronous and metachronous liver metastases were accepted and most patients had received preoperative

chemotherapy. The first six patients received a reduced 5-FU dosage (250 mg/m^2), and an independent safety committee gave permission to escalate to full dosage. Twenty-four patients were randomized to receive 500 mg/m^2 5-FU either in combination with 60 mg/m^2 LV (LV60, n = 12), 30 mg/m^2 Arfo (A30, n = 6) or 120 mg/m^2 Arfo (A120, n = 6) as a bolus regimen (a slow i.v. injection for three minutes). Metastatic tissue was collected 60 minutes after folate administration, then 5-FU was given. After a 60-minute break, metastatic tissue was again collected. Folate levels and TS inhibition were determined by LC-MS/MS.

Results: The results showed that both A30 and A120 resulted in higher 5,10-methylenetetrahydrofolate (CH_2-THF) concentrations in metastases, both before ($p = 0.037$ and $p = 0.0003$, respectively) and after ($p = 0.031$ and $p = 0.0023$, respectively) 5-FU treatment, as compared to LV60. Administration of A30 or A120 resulted in a higher ratio of poly/monoglutamated folates compared to LV60 after 5-FU administration ($p = 0.045$ and $p = 0.0049$, respectively). A dose-dependent TS inhibition was seen after administration of A30 (54.2% ± 189) vs A120 (83.8% ± 431) and both A30 and A120 seemed to give a better mean TS inhibition than LV60 (25.4% ± 301, $p = 0.081$ and $p = 0.0026$, respectively). The perioperative chemotherapy was well tolerated, and no Suspected Unexpected Serious Adverse Reaction occurred.

Conclusions: Significantly higher CH_2-THF concentration, ratio of poly-/monoglutamated CH_2-THF, and TS inhibition was found in colorectal liver metastases in patients receiving bolus injections of Arfo compared to standard bolus LV therapy. Thus, the results of the Modelle-001 study suggest that treatment with 5-FU in combination with Arfo could lead to more effective clincal outcome which would be of great importance.