Folates in the Treatment of Colorectal Cancer

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i stora aulan, centralkliniken, Sahlgrenska Universitetssjukhuset/Östra, Göteborg fredagen den 5 december 2014, kl 09.00

av
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I. Taflin H, Wettergren Y, Odin E, Carlsson G, Derwinger K. Gene polymorphisms MTHFRC677T and MTRA2756G as predictive factors in adjuvant chemotherapy for stage III colorectal cancer. Anticancer Res. 2011 Sep:31(9):3057-62.

II. Taflin H, Wettergren Y, Odin E, Carlsson G, Derwinger K Folate Levels and Polymorphisms in the Genes MTHFR, MTR, and TS in Colorectal Cancer. Clin Med Insights Oncol. 2014 Feb:17(8):15-20.

III. Taflin H, Wettergren Y, Odin E, Derwinger K Folate levels measured by LC-MS/MS in patients with colorectal cancer treated with different leucovorin dosages. Cancer Chemoth Pharma. 2014 Sep 20. Epub ahead of print

IV. Wettergren Y, Taflin H, Odin E, Kodeda K, Derwinger K A pharmacokinetic and pharmacodynamic investigation of Modufolin® compared to Isovorin® after single dose intravenous administration to patients with colon cancer: a randomized study. Cancer Chemoth Pharm. 2014 Oct. 24. Epub ahead of print

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ABSTRACT

Folates in the Treatment of Colorectal Cancer
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Background: Colorectal cancer is one of the most common cancers in the world, and radical surgery with total removal of the tumour (RO-resection) is the single most important treatment. However, chemotherapy is recommended for patients with risk factors and patients with metastatic disease. 5-fluoruracil (5-FU) is the cornerstone of chemotherapy, used either as a single drug or in combination with other drugs. 5-FU it is almost always combined with the folate leucovorin (LV). The aim of this thesis was to examine the role of polymorphisms in genes involved in folate metabolism in relation to treatment and to examine the levels of various folate forms in the tumours, mucosa, and plasma of patients who received LV or Modufolin® which is the biological isomer of 5,10-methylenetetrahydrofolate.

Methods: Polymorphisms in the methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), and thymidylate synthase (TYMS) genes were analysed using real-time PCR and TaqMan chemistry. The various folate forms were analysed in tumours, mucosa, and plasma using a sensitive liquid chromatography electrospray ionization tandem mass spectrometry technique.

Results: There was interdependency between polymorphisms in the MTFHR and MTR genes, which was associated with risk of side effects and overall survival in patients with stage III colorectal cancer receiving adjuvant chemotherapy. Total folate levels, all well as tetrahydrofolate (THF) and 5,10-methyleneTHF levels were significantly higher in tumours than in mucosa tissue. The individual variation in folate levels in both tumours and mucosa was greater than the variation found when the patients were subgrouped by gene polymorphisms. Only half of the patients who received 60 mg/m^2 LV had higher levels of 5,10-methyleneTHF in tumours than patients who received 0 mg/m^2 LV. Patients with rectal cancer had significantly lower levels of 5,10-methyleneTHF compared with patients with colon cancer. 5,10-methyleneTHF and THF concentrations were significantly higher in mucosa ($p<0.003$, both dosages) and tumours ($p<0.015$) 200 mg/m^2) after Modufolin® administration than after LV (Isovorin®) administration.

Conclusions: Polymorphisms in folate-associated genes can affect the risk that patients with colorectal cancer suffer from side effects during treatment with 5-FU-based chemotherapy. There is wide interindividual variation in 5,10-methyleneTHF levels in tumour tissue and mucosa after administration of standardised doses of LV. The doses of LV used in Nordic FLV-treatment may result in suboptimal levels of 5,10-methyleneTHF, especially in patients with rectal cancer. Modufolin® administration resulted in significantly higher 5,10-methyleneTHF levels than the natural l-form of LV, Isovorin®, and may potentially increase the efficacy of 5-FU-based chemotherapy.

Keywords: Folates, colorectal cancer, leucovorin, Modufolin®, polymorphisms, MTHFR; Methionine Synthase, TS, side effects, adjuvant chemotherapy LS-MS/MS

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