INTRODUCTION

The combination 5-fluorouracil (5-FU) and leucovorin (LV) has long been central in chemotherapy for colorectal cancer (CRC). Misregulation of 5-FU with LV increases the treatment response in 25–50% to about 25% LV, suggesting metabolic activation to the co-factor 5-LV/5-methyl-LV/5-formyl-LV. We have previously studied a postulated correlation between survival and expression of Folate pathway genes in stages III CRC treated with adjuvant FLV (5-FU + LV). Low expression of folate-related genes was linked to poor survival. In the present study, we aimed to study the expression of folate-related genes in synchronous mCRC (Stage IV).

PATIENTS AND METHODS

A total of 294 patients with mCRC receiving first-line treatment with bolus FLV, FLV + oxalipatinate (FLOX), or FLOX + LV were included. The patients were treated at the Sahlgrenska University Hospital, Gothenburg, Sweden, during 1995-2012, with the analysis performed in 2015. Patient and tumor characteristics are presented in Table 1. All tumors were classified according to the Tumor-Node-Metastasis (TNM) staging system when the patients were first diagnosed (index biopsy occasion). There were 51 patients with Stage I-III (mCRC) already at the biopsy occasion diagnosis (Tertile 1) (received surgery). There were 46 patients with Stage IV (mCRC) already at the biopsy occasion diagnosis (Tertile 2) (later referred to as Tertile 1 system). Tertile 3 (mCRC) patients initiated the start of treatment and the present follow-up. The patients were followed for a treatment-free period of three years or until disease progression or death. PFS was calculated from the date of treatment start to the last follow-up, or to the date of progression or death. Treatment with 5-FU and LV was considered to be equivalent to the use of the active LV-metabolite.

RESULTS

Among metastatic mCRC patients, only treatment and ECOG class, but no gene variable, had significant correlations with PFS (Table 5). Among synchronous patients there were several significant positive correlations between PFS and expression of several folate-relevant genes. Inclusion of the clinical covariates age, sex and tumor differentiation in the analysis did not significantly contribute to the multivariate prognostic model and the impact of ECOG and treatment only influenced the HR and p-values in a minor way.

Among synchronous patients, after adjustment for multiple testing in the Cox analysis of all gened expression, only MTHFD1L remained significant (p=0.0002). The MTHFD1L expression levels were divided into tertiles: low, intermediate and high levels. Patients in the intermediate and low tertile had lower survival and, when combined, had a median PFS of 6.3 months, compared to 101 months among patients in the high expression group (p=0.0002, Fig. 4).

The MTHFD1L protein is involved in outward transport of folates, and has preference for 10-formyl tetrahydrofolate, which inhibits the first conversion step of 5-LV. High expression of MTHFD1L may therefore decrease intracellular levels of 10-formyl tetrahydrofolate leading to a higher conversion rate of 5-LV to co-factor, and enhanced inhibition of THYME.

CONCLUSIONS

Folate-associated genes may predict response to treatment with FLV in stages III & IV CRC. The similar overall prognosis of the patients in the lowermost and medium tertiles is perhaps part of the explanation for the low overall response rates after treatment with FLV. It is interesting that the contribution of ABCC3 expression to the multivariate Cox model is more significant than that of MTHFD1L expression. However, the clinical impact on PFS is only minor. The MTHFD1L protein is involved in outward transport of folates, and has preference for 10-formyltetrahydrofolate, which inhibits the first conversion step of 5-LV. High expression of MTHFD1L may therefore decrease intracellular levels of 10-formyltetrahydrofolate leading to a higher conversion rate of 5-LV to co-factor, and enhanced inhibition of THYME.

REFERENCES & ACKNOWLEDGEMENTS

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Table 1: Genes selected for multivariate Cox model using PFS as dependent variable. Gene expression and clinical covariates were included one at a time (HR = Hazard Ratio).

Table 2: Cox proportional hazard regression models (HR = Hazard Ratio) using PFS as dependent variable. Gene expression and clinical covariates were included one at a time (HR = Hazard Ratio).

Table 3: Kaplan-Meier Curves showing PFS when patients with synchronous mCRC were stratified by tertiles. PFS (High expression (Tertile 1) = 5.685 – 6.461, Tertile 2/intermediate expression (Tertile 2) = 3.829 – 4.695, Tertile 3/low expression (Tertile 3) = 3.554 – 5.695).

Figure 1. Kaplan-Meier Curves showing PFS when patients with synchronous mCRC were categorized based on ABCR expression (Tertile High expression (Tertile 1) = 5.685 – 6.461, Tertile 2/intermediate expression (Tertile 2) = 3.829 – 4.695, Tertile 3/low expression (Tertile 3) = 3.554 – 5.695).

Figure 2. Kaplan-Meier Curves showing PFS when patients with synchronous mCRC were categorized based on MTHFD1L expression (Tertile High expression (Tertile 1) = 5.685 – 6.461, Tertile 2/intermediate expression (Tertile 2) = 3.829 – 4.695, Tertile 3/low expression (Tertile 3) = 3.554 – 5.695).

Figure 3. Kaplan-Meier Curves showing PFS when patients with synchronous mCRC were categorized based on MTHFD1L expression (Tertile High expression (Tertile 1) = 5.685 – 6.461, Tertile 2/intermediate expression (Tertile 2) = 3.829 – 4.695, Tertile 3/low expression (Tertile 3) = 3.554 – 5.695).