Letter to the Editor

Is thymidylate synthase a reliable predictor for response and survival during hepatic arterial infusion for hepatic metastases from colorectal cancer?

G Ferretti*,1, A Alimonti1 and F Cognetti1

Department of Medical Oncology, Division of Medical Oncology A, Regina Elena Cancer Institute Via Elio Chianesi 53, Rome 00144, Italy

Sir,

Decreased levels of the target enzyme thymidylate synthase (TS) have been repeatedly associated with superior clinical outcome in gastrointestinal cancers, including stomach cancer. In the study by Goekkurt et al (2006), patients who possessed a TS 5′ genotype associated with low TS mRNA expression levels showed a trend for superior survival time compared with those having TS genotypes associated with high TS mRNA expression. A significant association between clinical outcome to 5-fluorouracil (5FU)-based chemotherapy in colorectal cancer and TS polymorphisms was demonstrated when both TS polymorphisms within the 5′ untranslated (UTR) region were contemporarily analysed (Marcuello et al, 2004).

TS gene amplification and overexpression can lead to resistance to TS-targeting chemotherapeutic drugs (5FU and fluorodeoxyuridine (FUDR)) (Copur et al, 1995; Davies et al, 1999; Wu and Dolnick, 2003). Moreover, by hepatic arterial infusion (HAI) it is possible to reach lower TS mRNA and higher ribonucleotide reductase activity than with systemic chemotherapy (SC) (Kubota et al, 2002).

HAI therapy could generate higher intracellular levels of 5FU and FUDR metabolite, fluorodeoxyuridylate, locally (Gonen et al, 2003a). Among 135 patients randomly assigned to receive HAI vs systemic bolus 5FU and leucovorin, overall survival was significantly longer for HAI vs systemic treatment (P = 0.003), as was time to hepatic progression (P = 0.03) (Kemeny et al, 2006). By contrast, time to extrahepatic progression was significantly shorter in the HAI group (P = 0.02).

In a previous study, Gonen et al (2003b) reported that patients with resectable TS overexpressing (TS +) liver metastases from colorectal cancer have better overall survival (OS) when treated by HAI plus SC rather than by SC alone. On the contrary, patients with TS-negative metastatic colorectal cancer treated with SC plus HAI had similar OS compared with SC alone. More interestingly, in the study by Kemeny et al (2006), liver biopsies in the HAI group, although based on small numbers (40 patients), demonstrated that for patients with TS levels in tumour ≥ 4 the median OS was 14 months, while for those with levels less than 4, median OS was 24 months.

As previously reported (Alimonti et al, 2003), we think that, regarding patients treated with SC, it could be interesting to ascertain the role of the thymidine phosphorylase (TP), the first enzyme involved in the metabolic activation pathway of FU to fluorodeoxyribonucleotides. Conversely, continuous HAI of FUDR generates FUDR monophosphate via uptake and activation by thymidine kinase and, unlike i.v bolus 5FU treatment, levels of TP would not likely be of predictive value. Preoperative biopsies and resection specimens from patients with stage II/III rectal carcinoma receiving neoadjuvant 5FU-based chemoradiotherapy have been recently studied for TS and TP protein expression by immunohistochemistry, and results have been compared with histopathologic tumour regression. A significant association was observed between high TS expression in tumour biopsies as well as resection specimens and nonresponse of the tumour to therapy (P = 0.04), but low TP expression in the resection specimens was significantly associated with lack of response (P = 0.02) (Jakob et al, 2005). However, it is still controversial whether TP expression in tumour is an independent factor that adds to TS positivity in worsening the prognosis of patients with metastatic colorectal cancer.

Interindividual variation in the activity of metabolising enzymes can affect the extent of pyrimidine prodrug activation, acting on the efficacy of chemotherapy treatment (Maring et al, 2005). Patients with low levels of TP could be unable to properly metabolise FU administered by i.v. systemic infusion. A repeat polymorphism within the 5′ UTR, that alters TS expression, has been correlated with response and survival in colorectal cancer patients receiving 5FU in several studies (Iacopetta et al, 2001). Thus, the role of germline polymorphisms (uridine monophosphate kinase (UMPK), orotate phosphoribosyl transferase (OPRT), TS, dihydropyrimidine dehydrogenase (DPD), and methyltetrahydrofolate reductase (MTHFR)), tumour-specific somatic mutations and gene/protein expression levels (OPRT, UMPK, TS, DPD, uridine phosphorylase, uridine kinase, TP, thymidine kinase, deoxyuridine triphosphate nucleotide hydrolase) must be taken into account in explaining variation in anti-tumour efficacy and toxicity of 5F.

*Correspondence: Dr G Ferretti; E-mail: gia.fer@flashnet.it
Published online 17 October 2006
REFERENCES

Alimonti A, Ferretti G, Di Cosimo S, Cognetti F, Vecchione A (2003) Can colorectal cancer patients with thymidylate synthase-overexpressing liver metastases have an overall survival advantage with hepatic arterial infusion alone? J Clin Oncol 21: 3543 – 3544

Copur S, Aiba K, Drake JC, Allegre CJ, Chia E (1995) Thymidylate synthase gene amplification in human colon cancer cell lines resistant to 5-fluorouracil. Biochem Pharmacol 49: 1419 – 1426

Davies MM, Johnston PG, Kaur S, Allen-Mersh TG (1999) Colorectal liver metastasis thymidylate synthase staining correlates with response to hepatic arterial floxuridine. Clin Cancer Res 5: 325 – 328

Goekkurt E, Hoehn S, Wolschke C, Wittmer C, Stueber C, Hossfeld DK, Stoehlmacher J (2006) Polymorphisms of glutathione S-transferases (GST) and thymidylate synthase (TS)-novel predictors for response and survival in gastric cancer patients. Br J Cancer 94(2): 281 – 286

Gonen M, Banerjee D, Bertino J, Kemeny N (2003a) In reply. J Clin Oncol 21: 3544 – 3545

Gonen M, Hummer A, Zervoudakis A, Sullivan D, Fong Y, Banerjee D, Klimstra D, Gordon-Cardo C, Bertino J, Kemeny N (2003b) Thymidylate synthase expression in hepatic tumors is a predictor of survival and progression in patients with resectable metastatic colorectal cancer. J Clin Oncol 21: 406 – 412

Jacopetta B, Grieu F, Joseph D, Elsaleh H (2001) A polymorphism in the enhancer region of the thymidylate synthase promoter influences the survival of colorectal cancer patients treated with 5-fluorouracil. Br J Cancer 85: 827 – 830

Jakob C, Liersch T, Meyer W, Barett GB, Hausler P, Schwabe W, Becker H, Aust DE (2005) Immunohistochemical analysis of thymidylate synthase, thymidine phosphorylase, and dihydropyrimidine dehydrogenase in rectal cancer (cUICC II/III): correlation with histopathologic tumor regression after 5-fluorouracil-based long-term neoadjuvant chemoradiotherapy. Am J Surg Pathol 29: 1304 – 1309

Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, Weeks JC, Sigurdson ER, Herndon 2nd JE, Zhang C, Mayer RJ (2006) Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol 24(9): 1395 – 1403

Kubota T, Watanabe M, Otani Y, Kitajima M, Fukushima M (2002) Different pathways of 5-fluorouracil metabolism after continuous venous or bolus injection in patients with colon carcinoma: Possible predictive value of thymidylate synthetase mRNA and ribonucleotide reductase for 5-fluorouracil sensitivity. Anticancer Res 22: 3537 – 3540

Marcuello E, Altes A, del Rio E, Cesar A, Menoyo A, Baiget M (2004) Single nucleotide polymorphism in the 5’ tandem repeat sequences of thymidylate synthase gene predicts for response to fluorouracil-based chemotherapy in advanced colorectal cancer patients. Int J Cancer 112: 733 – 737

Maring JG, Groen HJ, Wachters FM, Uges DR, de Vries EG (2005) Genetic factors influencing pyrimidine-antagonist chemotherapy. Pharmacogenom J 5: 226 – 243

Wu Q, Dolnick BJ (2003) Detection of thymidylate synthase modulators by a novel screening assay. Mol Pharmacol 63: 167 – 173