

CHEMOTHERAPY

Predictors of chemotherapy response in advanced CRC

Researchers have now shown that immunohistochemical analysis of excision repair cross-complementing 1 (ERCC1) and thymidylate synthase might be a useful prognostic predictor in patients with advanced colorectal cancer (CRC). One of the first-line treatments for patients with advanced CRC is 5-FU in combination with oxaliplatin. Although this regimen prolongs survival and time-to-disease progression, there is variability in patient response, which may be attributed to a variety of factors. For instance, resistance to platinum compounds has been associated with increased DNA repair and alterations in the glutathione metabolic pathway. Elevated thymidylate synthase expression might confer resistance to fluoropyrimidines. In this context, identifying potential prognostic markers in these pathways may help predict response to chemotherapy.

Kim *et al.* investigated whether ERCC1, thymidylate synthase and glutathione

S-transferase π (GST π) expression could be useful in the prediction of clinical outcome.

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The researchers assessed 70 patients with advanced CRC treated with 5-FU and oxaliplatin. Immunohistochemical analysis revealed that 55.7%, 68.6% and 71.4% of the tumor samples were positive for ERCC1, thymidylate synthase and GST π expression, respectively. Patients with tumors that did not express thymidylate synthase responded to chemotherapy. Inhibition of thymidylate synthase is one of the main mechanisms of action of 5-FU and previous findings in rectal, gastric, head and neck tumors have correlated thymidylate synthase

overexpression with 5-FU resistance. Although there were no significant differences between response to treatment and ERCC1 or GST π expression, the median overall survival was significantly longer in patients without ERCC1 expression. Likewise, in non-small-cell lung and gastric cancer, low ERCC1 expression has been linked to prolonged survival following cisplatin-based chemotherapy. Furthermore, Kim *et al.* observed poor overall survival in patients with ERCC1 and thymidylate synthase or ERCC1, thymidylate synthase and GST π positive tumors, and multivariate analysis revealed that ERCC1 and thymidylate synthase expression had a significant effect on overall survival.

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Original article Kim, S. H. *et al.* Prognostic value of ERCC1, thymidylate synthase, and glutathione S-transferase pi for 5-FU/oxaliplatin chemotherapy in advanced colorectal cancer. *Am. J. Clin. Oncol.* **32**, 38-43 (2009).