Highlights from this issue

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Luminal GI

Validation of a novel endoscopic classification and grading system for eosinophilic oesophagitis

Currently, there is limited consensus on how best to characterise the endoscopically identified oesophageal features in eosinophilic oesophagitis (EoE). In this issue of *Gut* Hirano *et al* propose a system incorporating standardised classification and grading of severity. The proposed classification and grading system demonstrated good interobserver agreement among paediatric and adult gastroenterologists with varying degrees of clinical experience with EoE. This instrument will facilitate comparisons of clinical phenotypes of patients with EoE among gastroenterologists. Further studies are needed to assess if the proposed system predicts clinical severity and is an important outcome in determining the response to medical or dietary treatment of eosinophilic oesophagitis.

The next iteration of precision medicine for cancer care

Our ability to treat metastatic colorectal cancer has improved in the last 10 years partly because of the development of targeted therapies directed at the epidermal growth factor (EGF) receptor, such as cetuximab. However, a substantial

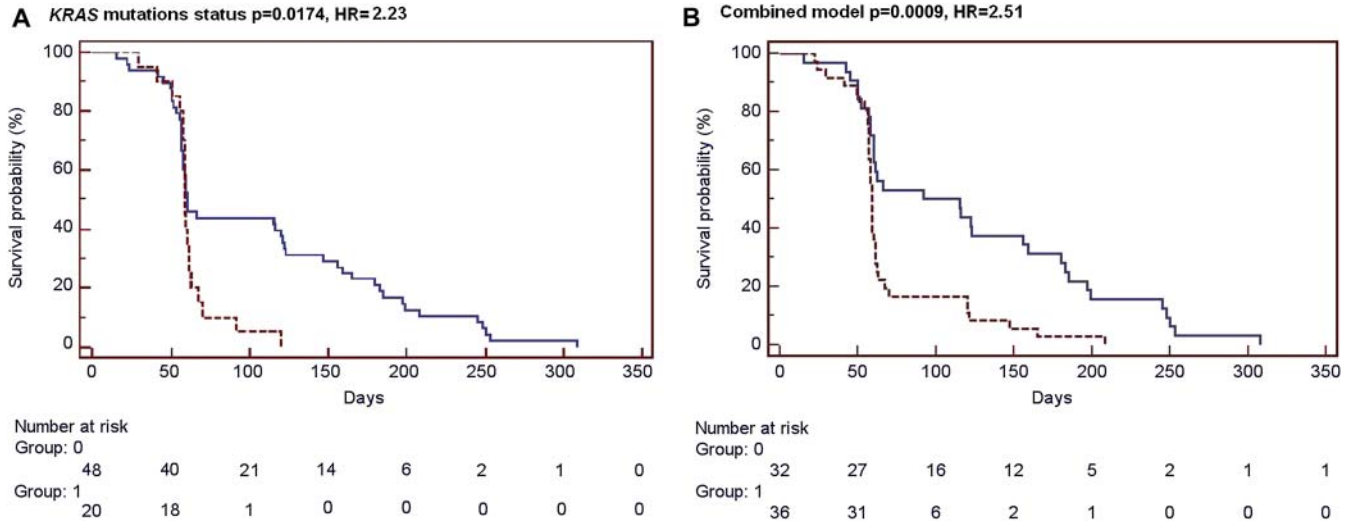

Figure 1 (A and B) Classification by *the combined signature* is associated with response to cetuximab treatment: Kaplan-Meier survival analysis of 68 metastatic colorectal cancer patients who have received cetuximab treatment. Tumour samples have been classified *in silico* as wildtype-like (Group 0, blue solid line) or as oncogenic (Group 1, red dashed line) by the (A) *KRAS* mutation status, by (B) the combined signature model.

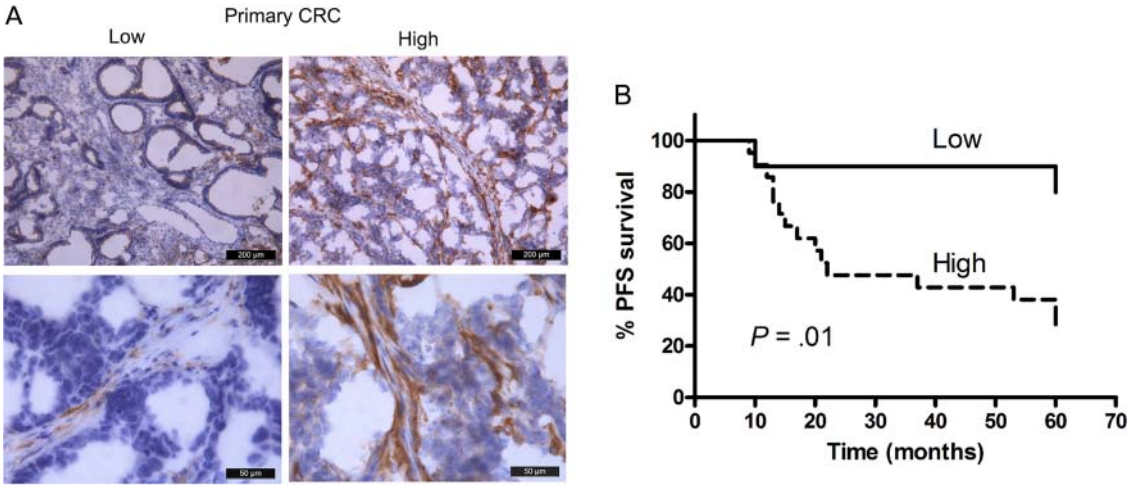

Figure 2 (A and B) Expression of tNRG1 in primary human colorectal cancers (CRCs) (A) Representative tNRG1 stained CRC samples that illustrate IHC scores of low and high expression (upper panel). Expression levels of tNRG1 in normal and CRC tissue and associations of tNRG1 IHC scores with invasion depth and UICC stage (lower panel). (B) Kaplan-Meier graph showing difference in 5-year progression free survival between patients whose tumours have high (n=21) and low (n=10) tNRG1 expression in T-MC.

Table 1 Multivariate analysis for estimation of the chemopreventive effect of metformin in diabetic patients

Diabetic patients (N=47 820)	ORs (95% CI)	p Value
Metformin use (user vs non-users)	0.79 (0.75 to 0.83)	<0.0001
Age (each incremental year)	1.00 (1.00 to 1.00)	0.3031
Gender (male vs female)	1.06 (1.01 to 1.11)	0.0216
Hepatitis B	14.58 (13.28 to 16.02)	<0.0001
Hepatitis C	18.02 (16.40 to 19.79)	<0.0001
Liver cirrhosis	3.14 (2.62 to 3.75)	<0.0001
End stage renal failure	0.68 (0.63 to 0.73)	<0.0001
DM duration (each incremental year)	0.92 (0.91 to 0.93)	<0.0001
DM control (each incremental visit per year)	1.00 (1.00 to 1.01)	0.6694
Other OHA agents use (users vs non-users)	1.20 (1.10 to 1.30)	<0.0001
Thiazolidinediones use (users vs non-users)	0.76 (0.70 to 0.81)	<0.0001
Insulin use (users vs non-users)	4.37 (4.17 to 4.59)	<0.0001

DM, diabetes mellitus; OHA, oral hypoglycaemic agent.

number of patients do not respond to these therapies, often because of oncogenic mutations in genes that activate the EGF pathway downstream of the EGF receptor. These genes include *KRAS, BRAF,* and *PIK3CA,* among others. Capella and colleagues have now conducted a study that has identified a pattern of genes that are induced by activation of this pathway and that predict the likelihood that a patient's cancer will respond to cetuximab (see figure 1). Their study reveals that there is a convergence of oncogenic mutations in genes downstream of EGFR at the transcriptional level that allows the identification of patients with an active EGFR signalling pathway that could benefit from downstream pathway inhibition.

Colorectal cancer co-opts the patient into fuelling its growth

It has been shown in model systems that bone marrow-derived mesenchymal stem cell (BM-MSC) migrate to primary tumours and help drive tumour progression. De Wever and colleagues have conducted an elegant series of studies that demonstrate BM-MSCs promote tumour progression by secreting a growth factor called neuregulin,(NRG1) which stimulates the HER2/HER3 receptors on the cancer cells and induces the tumour promoting PI3K signalling pathway in these cells. They also found that high neuregulin levels in the tumour associated with poor prognosis (see figure 2). Their studies raise the possibility that colorectal cancers with high NRG1 levels may be effectively treated with anti-HER2 treatments, such as Herceptin.

Hepatology

Metformin for prevention of hepatocellular carcinoma—new insights

Diabetes mellitus is a risk factor for hepatocellular carcinoma (HCC). Clinical observational studies suggest that metformin reduces the HCC risk. This interesting nationwide population study from Taiwan ***(see page 606)*** shows that metformin decreases the risk of HCC in a dose-dependent manner by seven percent every year of administration. This effect is independent of confounding factors (Table 1). Furthermore, the paper provides important new insights into the antitumoral actions of metformin: inhibition of hepatoma cell growth via cell cycle arrest. Interestingly metformin enhanced tumour inhibition by doxorubicin in an in vivo model. This may open new perspectives for the treatment of HCC.

Novel stategies to prevent thioguanine—induced liver injury

Thiopurines have been established for the treatment of inflammatory bowel diseases. Among those 6-thioguanine (6TG) exhibits excellent pharmacokinetic and pharmacodynamic properties. Unfortunately, serious liver injury, such as sinusoidal obstruction syndrome (sos) and nodular regenerative hyperplasia have been observed in patients taking 6TG. This comprehensive study from Australia ***(see page 594)*** employed a novel murine model to analyse the hepatic adverse effects of 6TG. They demonstrated that sos was dose-dependent and mediated by hepatic sinusoidal endothelial cell activation. Importantly, avoiding high peak doses of 6TG by twice daily dosing markedly reduced liver injury (figure 3A) while still being effective for the treatment of colitis. These findings could have great translational impact.

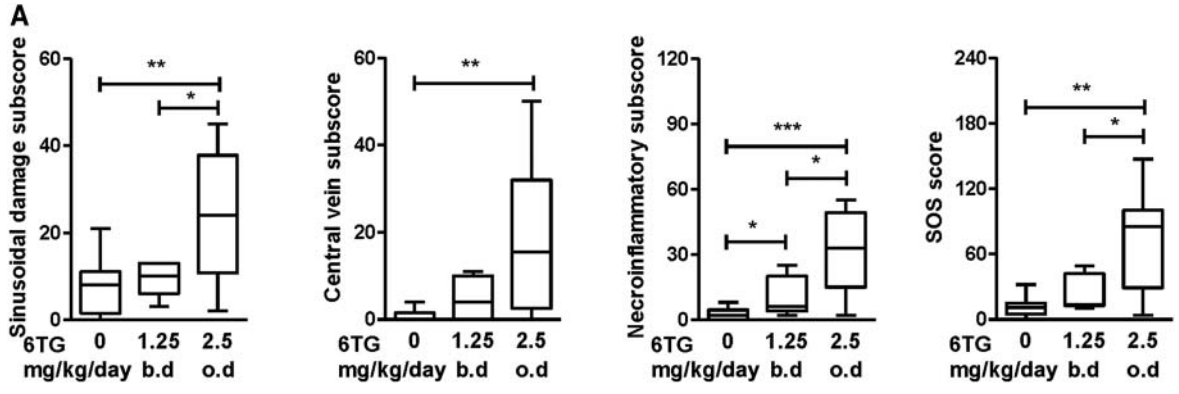

Figure 3 (A) Split dosing (twice daily 1.25 mg/kg) of thioguanine (6TG) reduces liver injury.