Highlights from this issue

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Practice guidance on managing GI problems resulting from cancer treatment

The last 3 decades have seen a threefold increase in the numbers of survivors of cancer. Chronic gastrointestinal side effects are a common cause of morbidity and reduced quality of life. Side effects of treatment are frequently missed or overlooked because the current priority of cancer follow-up is to perform surveillance for recurrent cancer. Individual GPs are unlikely to have many patients with complex problems after cancer therapy and so will require guidance if these patients are to be optimally managed. Symptoms can often be alleviated or cured. In view of the urgent need for guidance on how to manage such patients, the President of the British Society of Gastroenterology commissioned this landmark document following a request from Professor Sir Mike Richards, National Cancer Director, and Professor Jane Maher, Chief Medical Officer of Macmillan Cancer Support and Chair of the National Cancer Survivorship Initiative's Consequences of Treatment Group. The authors of the document, Andreyev and colleagues, are to be congratulated for producing an outstanding account of the clinical problems and their management. This is an area of clinical medicine that is poorly researched yet affects millions of patients on a global scale. *Gut* has taken the lead on making this a key research priority and we hope the next few years will see the high quality studies that will provide the necessary evidence base for future guidelines (see page 179).

Thiopurines protect against colorectal cancer in IBD patients

5-amino salicylates (5-ASA) reduce the risk of colorectal cancer in IBD patients, possibly due to their anti-inflammatory properties but thiopurines are not regarded as chemopreventive agents. On the contrary, there is anxiety about their long-term use due to the reported increased risk of extra-intestinal malignancies. In this issue of *Gut*, van Schaik *et al* investigated the association between

Figure 1 Kaplan-Meier curves comparing the development of AN in each treatment group (log-rank test $p=0.04$). Patient that develop AN are censored at the moment AN is detected. Vertical lines represent events of AN.

thiopurine or 5-ASA use and the risk of advanced neoplasia (AN), including high-grade dysplasia and colorectal cancer, in a large cohort of patients with IBD in The Netherlands. A total of 2578 patients with IBD were included. Thiopurine use was associated with a significantly decreased risk of developing AN (adjusted HR 0.10, 95% CI 0.01 to 0.75). 5-ASA therapy also had a protective effect on developing AN, but this was not statistically significant

(adjusted HR 0.56, 95% CI 0.22 to 1.40) (see figure 1). This chemopreventive effect of thiopurines might provide an extra incentive to prescribe these drugs in IBD patients, especially in those with colonic disease (see page 235).

Can telomeres tell us who is at risk for colorectal cancer?

Telomeres act as caps on the ends of chromosomes to preserve the stability of chromosomes during DNA replication. Telomeres gradually shorten as we age and are believed to play an important role in the ageing process. Shorter telomeres have also been associated with an increased risk of malignancy, including colorectal cancer. Telomere length is heritable and may be an intermediate phenotype linked to genetic susceptibility to colorectal cancer. Jones *et al* now show that there are variants in the sequence of DNA, called single nucleotide polymorphisms (SNPs) that associate with an increased risk of colorectal cancer and, surprisingly, longer telomeres. This is an unexpected finding and suggests that long telomeres may predispose to colorectal cancer by promoting the

Figure 2 Models of associations between telomere length and colorectal cancer risk.

Figure 3 Loss of *Lkb1* induces changes in Renin expression. (A). Renin and Muc2 co-localisation in the goblet cells of control (+/+) and recombined small intestine (-/-).

immortalisation of tumours arising in these people. These results show that telomere biology is likely complicated and will require extensive study before it can be used clinically (see figure 2) (see page 248).

A new way to treat cancer?

Mutations in the *LKB1* tumour suppressor are a cause of Peutz-Jeghers syndrome, which is characterised by gastrointestinal hamartomatous polyps and a predisposition to a variety of cancers. It is also important in the formation of a variety of sporadically occurring tumours. It is known to affect tumour formation by deregulating the metabolism of tumour cells by enhancing the mTor signalling pathway (see figure 3). In this issue of *Gut*, Shorning *et al* demonstrate that inactivation of *LKB1* may also promote tumour formation by affecting the renin-angiotensin system, which controls apoptosis, cell growth and differentiation as well as ion absorption, and glucose and cholesterol metabolism. They found that deletion of *Lkb1* in a mouse model increased renin and angiotensin levels, most likely as a consequence of *Lkb1* serving as a checkpoint protein for cellular events directed by the MAPK signalling

pathway. These findings suggest that therapies directed at the rennin-angiotensin pathway may be a novel treatment for Peutz-Jeghers syndrome and tumours carrying *LKB1* mutations (see page 202).

Hepatology

MicroRNA as new prognostic marker and therapeutic target in hepatocellular carcinoma

MicroRNAs (miRNAs) are short RNAs which suppress protein expression. There

Figure 4 Kaplan-Meier analysis for HCC patient survival as a function of miR-124 levels. Probability of patient survival: high-expression of miR-124, $n=65$; low-expression of miR-124, $n=66$ ($p<0.001$).

is increasing evidence for a role of specific miRNAs in HCC. This interesting study from China confirmed the downregulation of miR-124 in HCC cell lines and human HCC tissues. They showed that low expression of miR-124 is associated with more aggressive HCC biology and poor prognosis (see figure 4). Moreover they demonstrated direct effects of this miRNA on rho-kinase 2 and EZH2 genes, respectively. Altogether, these results suggest miR-124 as prognostic marker and potential therapeutic target in HCC (see page 278).

Hepatitis C triple therapy will markedly increase number of treated patients and costs

Combination therapy adding protease inhibitors to the established combination of pegylated interferon and ribavirin has just been approved by European and USA regulatory bodies for the treatment of patients with hepatitis C genotype 1. Triple therapy markedly increases sustained viral response in treatment-naïve, but also in pretreated patients. Thus one may expect an increasing demand for this novel standard of care. This intriguing study from France used a model based analysis with a detailed decision tree and three different scenarios to estimate the number of patients requesting treatment in France in 2012 under the new auspices.

According to their most conservative scenario they estimate an additional ten thousand patients (see table 1). This represents a major organisational challenge and financial burden with associated costs of around 500 million Euros (see page 290).

Table 1 Estimated number of genotype 1 HCV patients treated in France in 2010 and 2012 at unchanged screening rate

	Treated in 2010*	To be treated in 2012† Scenario 1
Naïve	3,200	5,500
F0-F2	2,500	3,600
F3-F4	700	1,900
Experienced	1,900	9,500
F0-F2	1,300	5,100
F3-F4	600	4,400
Total	5,100	15 000

*With PEG-IFN/RBV.

†With PEG-IFN/RBV+PI with the exception of 10% of treatment-naïve, F0-F2 patients who will be treated with PEG-IFN/RBV.