Alpha interferon in disseminated carcinoid

Alpha interferon in disseminated carcinoid

Current treatment for midgut carcinoid includes radical surgery of the primary tumour, resection of lymph node metastases and resection of liver metastases. In the presence of disseminated disease however, cure is unusual. Palliative liver resection and hepatic artery embolisation are also recognised to decrease hormone secretion and reduce tumour volume. Somatostatin analogues reduce the synthesis and secretion of neuroendocrine cells so reducing hormonal symptoms in up to 80% of patients. Alpha interferon has been previously shown to reduce urinary 5HIAA levels in carcinoid patients. In a previous Norwegian study a survival advantage was shown for patients treated with alpha interferon in combination with hepatic arterial embolisation. This present study was therefore carried out to identify the effect of alpha interferon added to a somatostatin analogue on survival and tumour progression after initial tumour resection and embolisation for disseminated mid gut carcinoids. Sixty eight patients were treated with maximum tumour reduction and underwent hepatic artery embolisation followed by randomisation to either treatment with octreotide or a combination of octreotide and alpha interferon. All patients had liver metastases. The overall five year survival rate was 66%. Although there was no significant difference in survival between patients treated with octreotide alone (five year survival rate 37%) and those given octreotide in combination with alpha interferon (five year survival rate 57%), patients treated with alpha interferon had a significantly reduced risk of tumour progression during follow up (p = 0.008). This was a relatively small but very important study which demonstrates that alpha interferon may have a role in inhibiting tumour growth in patients with disseminated midgut carcinoid who have undergone debulking surgery and hepatic embolisation. Hopefully further larger studies with quality of life assessments included will be forthcoming.

European experience of 6-thioguanine for azathioprine intolerance in Crohn’s disease differs from US reports

Azathioprine intolerance affects up to a quarter of patients treated. While its metabolite 6-mercaptopurine may then be tolerated by some, an alternative is treatment with active thioguanine nucleotide metabolites represented by 6-thioguanine (6-TG). Initial reports of good tolerance of 6-TG from Cedars Sinai (Dubinsky et al, 2001) were followed at this year’s DDW by a report from the same group of frequent hepatotoxic reactions. This multicentre open-label study from Germany recruited 37 patients with chronic active Crohn’s disease. Treatment with 6-TG 40 mg/day for 24 weeks (with a dose escalation to 80 mg/day after 12 weeks if unresponsive), lead to response in 57% and remission in 35%. Only 1/12 responded to dose escalation. 6-TG was tolerated by 12/16 intolerant of azathioprine and was more effective in this group. 6-TG was discontinued in 6/37, two because of leucopenia, but only two had transient elevation in liver enzymes that resolved without dose reduction. Other side effects included pancreatitis, photosensitivity, and headaches.

This is encouraging, because azathioprine intolerance in steroid-dependent or steroid-refractory Crohn’s disease is a major therapeutic dilemma. It is also consistent with another European report on 6-TG (dose 20-40 mg in 32 patients), given for eight weeks without hepatotoxicity (Derijks et al, 2003). Nevertheless, it is at odds with some US experience, where 6-TG has rapidly fallen out of favour because a quarter had rises in ALT (median 39iu), drop in platelet count of 115×10^9/l and 76% of these had evidence of nodular regenerative hyperplasia on biopsy (Dubinsky et al, Gastroenterology 2003;124:A8). The reason for the trans-Atlantic difference is unclear. It is unrelated to the serum concentration of 6-TG. Haematologists, who have used 6-TG for decades, certainly recognise an association with portal hypertension. The message seems to be: proceed with caution, monitor liver function and platelet count, but do not yet discard 6-TG for patients who are azathioprine-intolerant, steroid-refractory and for whom surgery or methotrexate are not options.

Time for a paradigm shift?

Coeliac disease (CD) has been described as the playground of the immunologists but with the introduction of accurate serological screening tests, rising prevalence estimates, and calls for mass screening, space may need to be found for epidemiologists and public health specialists.

Maki and colleagues screened serum samples collected in 1994 from 3654 Finnish schoolchildren (aged 7–16 years). In 2001 the samples were tested for endomysial and tissue transglutaminase antibodies and those with tests suggestive of CD were invited for investigation. Results of the two antibody tests were highly concordant. Of 56 (1.5%) with positive serology 10 had already been diagnosed as having CD between 1994 and 2001 and 10 declined small bowel biopsy. Of the remainder 27 had CD confirmed by duodenal biopsy giving an overall prevalence of one in 99 children. Remarkably, of nine children deemed to have positive serology in 1994 on retesting in 2001, seven had normal serology and normal biopsies while two continued to have abnormal serology but had normal biopsies. As expected, HLA typing showed a strong association with the DR3-DQ2 haplotype with an odds ratio of 26, but even so 18% of all Finnish children were of this haplotype. In an accompanying editorial Fasano makes a case for population screening referring to the substantial morbidity of undetected CD, but as yet evidence for this is lacking.

While a 1% prevalence of CD in Finnish children is in line with estimates from other European countries including the UK, the approximately 10% of seropositive children who become seronegative challenges the “once a coeliac, always a coeliac” dogma. It would have been interesting to have re-tested the seronegative as well as the seropositive children. This paper will provide ammunition for both the protagonists and antagonists of population screening for CD.

Sigmoidoscopy screening for colorectal cancer—what are we missing?

The UK Department of Health is currently deciding on the most appropriate strategy for colorectal cancer screening. The UK faecal occult blood (FOB) pilot data have been published in July 2003 and
results look promising. The main alternative in the UK is flexible sigmoidoscopy (FS) screening. This has the potential to save more lives than FOBT screening but evidence of efficacy is still awaited. One of the main questions is how often participants should be screened with FS. Schoen et al report results from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial in 9317 subjects with an initial negative FS returning three years later. 1292 (13.9%) had a polyp or mass detected at repeat FS and in 292 (3%) this was an adenoma or cancer. The initial FS examination had been adequate in 81% of cases where subsequent neoplastic lesions were found. The authors suggested these data support frequent surveillance intervals for FS.

Only 6/9317 (0.06%) had colorectal cancer and 44/9317 (0.5%) had adenomas >1 cm so the pick up rate for clinically serious lesions is modest. It is therefore uncertain whether advocating FS every three years is cost effective. This study does however demonstrate that all tests are fallible and this must be emphasised to subjects attending screening.

References