Family history linked to lower risk of colorectal cancer recurrence

Patients with stage III colon cancer who have a family history of colorectal cancer in a first-degree relative have a lower risk of recurrence and death than those without, according to a major study looking at the link between inherited colorectal cancer and survival (Chan et al, 2008).

As many as 20% of patients with colorectal cancer has a first-degree relative who also has the disease. Studies have shown that a history of colorectal cancer in a first-degree relative nearly doubles the risk of developing the disease. However, the influence of family history on cancer recurrence and survival has previously been unclear.

The study followed up 1087 patients with stage III colon cancer who were taking part in a clinical trial of chemotherapy. Rates of recurrence and death over a median follow up of 5.6 years in 195 patients (17.9%) with a family history of colorectal cancer in a first-degree relative were compared with the 892 patients without a close relative with the disease.

Cancer recurrence or death occurred in 29% of patients with a family history of colorectal cancer compared to 38% of those without a first-degree relative with the condition. The risk of recurrence was 26% lower, while their risk of death was 25% lower.

The reduction in risk of cancer recurrence or death became stronger as the number of affected first-degree relatives increased. Compared to those without a family history, patients with one affected relative had a 23% greater disease-free survival, increasing to 51% in those with two or more affected relatives.

Improved disease-free survival was independent of measures of gene damage – microsatellite instability and mismatch repair proteins MLH1 and MSH2 – commonly found in inherited colorectal tumours.

Lead author Dr Jennifer Chan (Dana-Farber Cancer Institute, Boston, US) commented: 'Among patients with stage III colon cancer receiving adjuvant chemotherapy, a family history of colorectal cancer is associated with a significant reduction in cancer recurrence and death. This finding may reflect a distinct underlying molecular and pathogenic mechanism in cancers that develop in the setting of a common family history.'

In an editorial accompanying the report (Pasche, 2008), Dr Boris Pasche (Northwestern University Feinberg School of Medicine, Chicago, US) noted that analyses of molecular predictors of survival after adjuvant chemotherapy for colon cancer have shown that loss of chromosome 18 correlates with a poor prognosis.

He suggested that the next obvious step would be to determine whether loss of chromosome 18 is less common in the tumours from patients with a family history of colorectal cancer. 'If these intriguing findings are validated in other studies, family history may well become a new prognostic factor in colorectal cancer,' he said.

Stephen Pinn

Chan JA, Meyerhardt JA, Niedzwiecki D et al (2008) Association of family history with cancer recurrence and survival among patients with stage III colon cancer. *JAMA* **299**: 2515–23

Pasche B (2008) Familial colorectal cancer. A genetics treasure trove for medical discovery. *JAMA* **299**: 2564–5

First pegylated anti-TNF for rheumatoid arthritis

An application for marketing authorization for a new anti-tumour necrosis factor (TNF) therapy has been made by UCB.

The European Medicines Agency accepted UCB's request for approval of certolizumab pegol (Cimzia) as a subcutaneous treatment for adults with moderate to severe rheumatoid arthritis in July. If approved, certolizumab will be the first pegylated anti-TNF available in Europe for rheumatoid arthritis.

The move follows a filing to the US Food and Drug Administration for approval of certolizumab to treat rheumatoid arthritis. The Food and Drug Administration approved certolizumab for treatment of Crohn's disease in adults in April.

Commenting on the development, Professor Paul Emery, ACR Professor of Rheumatology at Leeds University, told the *British Journal of Hospital Medicine*: 'If this treatment is approved, it will be a useful addition to current treatment options for rheumatoid arthritis patients because only around 50% of patients respond to their first anti-TNF.'

In addition, Professor Emery said that data show the drug has a rapid onset of action, which is a useful feature in context of helping rheumatoid arthritis patients stay in work. Data presented at EULAR in Paris in June suggested that certolizumab improved work productivity in patients with active rheumatoid arthritis compared to placebo.

The data were based on an analysis of patients receiving certolizumab treatment in the RAPID-1 and RAPID-2 trials, which showed that certolizumab together with methotrexate improved the signs and symptoms of rheumatoid arthritis as early as the first week of treatment and inhibited progression of structural damage.

The analysis of work performance found that certolizumab-treated patients reported a decrease in days with reduced productivity (2.3 days per month *vs* 1.5 days) compared to controls.

Rhonda Siddall

Reduced rate of decline in lung function

Treatment with Seretide (salmeterol/fluticasone propionate) significantly lowers the rate of lung function decline in patients with chronic obstructive pulmonary disease (COPD).

Treatment can decrease the excess decline in lung function by more than 50%, as measured by forced expiratory volume in 1 second.

Professor Peter Calverley, Professor of Respiratory Medicine at the University of Liverpool and lead author, said that this is 'the first clear evidence that treatment of symptomatic COPD patients with long acting beta agonists and/or inhaled corticosteroids slows the progression of the disease.'

Celli BR, Thomas NE, Anderson JA et al (2008) Effect of pharmacotherapy on rate of decline of lung function in COPD: results from the TORCH study. *Am J Respir Crit Care Med* **178**(4): 332–8

Sorafenib reduces risk of death from liver cancer

Results of the Sorafenib HCC Assessment Randomized Protocol (SHARP) phase III trial have demonstrated that treatment of primary liver cancer with sorafenib results in a 31% relative reduction in the risk of death. The results were published in the *New England Journal of Medicine* (Llovet et al, 2008).

'For the first time we have unequivocal evidence of a treatment that significantly improves the survival of patients with advanced hepatocellular carcinoma,' said Dr Daniel Palmer, Senior Lecturer in Medical Oncology, University of Birmingham.

But Dr Palmer added that there were challenges ahead: 'We need to find ways of identifying in advance those patients most likely to benefit from this treatment and to ensure that equitable access to the drug can be achieved for all those for whom this treatment is indicated.'

The SHARP trial evaluated 602 primary liver cancer patients who had no prior systemic therapy.

Median overall survival was 10.7 months for patients who received sorafenib compared to 7.9 months for patients who received placebo (hazard ratio=0.69; $P<0.001$). There was no difference in time to symptomatic progression between patient groups, based on a patient-reported assessment questionnaire.

Median time to tumour progression was 5.5 months with sorafenib *vs* 2.8 months with placebo (hazard ratio=0.58; $P\leq0.001$). The most commonly observed serious adverse events in patients receiving sorafenib were diarrhoea and hand-foot-skin reaction.

Professor Will Steward, Head of the Department of Cancer Studies and Molecular Medicine at the University of Leicester, said: 'The SHARP study highlights that sorafenib is the first drug to significantly improve survival in advanced liver cancer. It does so without detriment in producing serious toxicity and reducing quality of life.'

Rhonda Siddall

Llovet JM, Ricci S, Mazzaferro V et al for the SHARP Investigators Study Group (2008) Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* **359**(4): 378–90

Professor Will Steward, Head of the Department of Cancer Studies and Molecular Medicine, University of Leicester

New agent may improve executive function in patients with Alzheimer's disease

New data suggest that two indicators of executive function in patients with Alzheimer's disease are improved by PBT2, an agent which reduces the levels of amyloid-beta in the spinal fluid (Lannfelt et al, 2008).

Amyloid-beta is thought to be toxic to brain cells and prevent them functioning correctly. PBT2 is said to work by interrupting the interaction between amyloid-beta and metal ions that are elevated in the brains of people with Alzheimer's disease.

Dr Lars Lannfelt (Uppsala University Hospital, Sweden) and Dr Craig Ritchie (Imperial College London, UK) and colleagues carried out a randomized trial to test the safety and efficacy of PBT2 in 78 patients with early Alzheimer's disease, aged 55 years or over. They also studied the effect of this agent on the biomarkers of Alzheimer's disease.

Two executive cognitive function tests showed improvement in patients randomized to a 250 mg dose of PTB2 compared to placebo ($P=0.041$ and $P=0.009$ respectively).

Furthermore, levels of amyloid-beta in the spinal fluid of those receiving active drug were reduced by 13% compared to placebo ($P=0.006$) at the end of the 12-week trial.

Commenting on the data, Professor Norman R Relkin (Memory Disorders Program, Weill Cornell Medical College, New York, US) said: 'If we assume that the amyloid hypothesis holds water, future clinical studies with PBT2 will provide the first real test of the importance of metal ion homeostasis in the pathogenesis of Alzheimer's disease.'

Stephen Pinn

Lannfelt L, Blennow K, Zetterberg H et al (2008) Safety, efficacy and biomarker findings of PBT2 in targeting Aß as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* **7**(9): 779–86 (epub 30 July)

Carers live in fear, survey shows

Most carers of people with lung conditions have no practical help at all, even though they are dealing with frightening attacks of breathlessness that need frequent hospitalization, according to a new survey by the British Lung Foundation.

More than a quarter (26%) of carers say a sudden worsening of symptoms such as extreme breathlessness has resulted in the person they care for being hospitalized at least six times in the past 5 years.

Cetuximab approved for metastatic bowel cancer

Patients with epidermal growth factor receptor-expressing metastatic colorectal cancer can now be treated with Erbitux (cetuximab), following European Commission approval.

Campaign calls for end to inequalities in Parkinson's disease

The European Parkinson's Disease Association called for an end to inequalities in care and treatment access for people with Parkinson's disease.

The plea was made during the launch of the campaign 'Parkinson's is visible, make it livable', intended to visualize the challenges faced by those with Parkinson's disease.

WORLD CONGRESS ON PAIN
GLASGOW, 19–21 AUGUST

Treatments are equally effective for postherpetic neuralgia

According to the first ever comparative study of topical and systemic treatments for neuropathic pain, 5% lidocaine medicated plaster (Versatis) is as efficacious as pregabalin (Lyrica) and is better tolerated.

These data were presented for the first time at the 12th World Congress on Pain and caused the Scottish Medicines Consortium to reverse an earlier negative decision and recommend the plaster for restricted use within NHS Scotland.

The open-label, multicentre study randomized over 300 patients with postherpetic neuralgia and diabetic polyneuropathic pain to 5% lidocaine medicated plaster or pregabalin.

The per protocol analysis conducted in 281 patients after the initial 4-week comparative phase of the study found similar response rates in the two groups (65.3% for topical treatment *vs* 62% for systemic treatment).

However, significantly fewer patients receiving topical treatment experienced overall adverse events (18.7% *vs* 46.4% for systemic treatment; $P \leq 0.0001$) and drug-related adverse events (5.8% *vs* 41.2% for systemic treatment; $P \leq 0.0001$).

Topical treatment was also associated with fewer adverse drug reactions leading to discontinuation (5.8% *vs* 25.5% for systemic treatment).

The lidocaine plaster is licensed for the treatment of neuropathic pain associated with previous herpes zoster infection. It became available in the UK in 2007, but has been used for nearly 10 years in the United States. Up to three plasters can be applied to the affected area for up to 12 hours followed by a plaster-free interval of at least 12 hours.

In an interview with the *British Journal of Hospital Medicine* in Glasgow, Professor Anthony Dickenson, Professor of Neuropharmacology, University College London, outlined the plaster's dual mode of action.

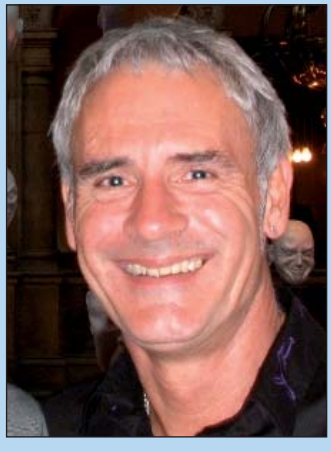
'Patients with nerve injury have an ongoing pain that may wax and wane, but one of their most problematic symptoms is allodynia, in which touch elicits very intense pain.

'The plaster provides an element of protection by providing a cooling cover over the painful area, but this is not the full explanation since the effects of the active plaster were significantly greater than placebo in the clinical trials.

'Lidocaine acts by blocking local sodium channels to prevent electrical impulses at the site of the injury from passing to the spinal cord and the brain, effectively attacking pain where it starts,' he explained.

Evidence-based recommendations (Dworkin et al, 2007) included both topical lidocaine and calcium channel alpha2-delta ligands such as pregabalin and gabapentin among first-line treatments for neuropathic pain. Tricyclic and serotonin and noradrenaline reuptake inhibitor antidepressants were other first-line recommendations.

Professor Anthony Dickenson, Professor of Neuropharmacology, University College London



Professor Dickenson concluded: 'The lidocaine plaster is probably first line if the patient has a localized, focal neuropathic pain. Choice also depends on the individual patient.

'The tricyclics are effective, but they are associated with side effects that could cause an elderly patient to fall. As a result, GPs tend to start with as low a dose as possible, but this may not be effective and so the patient may stop the treatment because it is not working. At least with the plaster you know that, if it is correctly positioned, the patient is receiving the right amount of drug.'

Sue Lyon

Dworkin RH, O'Connor AB, Backonja M et al (2007) Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* **132**(3): 237–51

Opioids dominate pain relief prescribing in emergency departments

Twice as many opioids than any other analgesic are prescribed or recommended for pain relief by accident and emergency doctors in Northern Ireland, according to findings from a multi-centre audit carried out in Northern Ireland.

A total of 1978 questionnaires were completed by health-care professionals during a 2-week period in June and July 2007 – including 471 from the four accident and emergency departments involved.

The most frequently prescribed analgesics were:

- Opioids (1181)
- Non-steroidal anti-inflammatory drugs (605)
- Non-opioids (341).

Of the opioids, co-codamol was prescribed 735 times, tramadol 233 times and co-dydramol 135 times; of the non-steroidal drugs, diclofenac was prescribed 268 times and ibuprofen 234 times, whereas the main non-opioid prescribed was paracetamol (313 prescriptions).

The most frequent indications for the prescription of analgesia were:

- Musculoskeletal pain (on 384 occasions)
- Backache (350)
- Osteoarthritis (340)
- Sprain or strain (162)
- Abdominal pain (88).

Stephen Pinn

World Congress on Pain
Glasgow, 19–21 August

Tapentadol a 'realistic alternative' to strong opioids for severe pain

The prospect of a realistic alternative to strong opioid analgesics for thousands of people throughout Europe who suffer from severe pain has moved a step closer with convincing evidence from a clutch of phase III clinical trials showing that a new agent, tapentadol IR (immediate release), minimizes gastrointestinal side effects while maintaining effective pain relief.

The data were presented for the first time at the World Congress on Pain. Approval for the use of tapentadol in Europe is now being sought from the regulatory authorities, with expectations of a licence in 2009.

The studies, ranging in duration from 10–90 days, involved 2155 patients diagnosed with severe, persistent or intermittent pain, including those with end-stage joint disease, acute pain following orthopaedic foot surgery, low back pain and osteoarthritis.

They showed that while tapentadol IR (50 mg and 75 mg doses) was similar to a classic opioid analgesic, oxycodone IR (at the standard 10 mg dose) in terms of sustained efficacy, the incidence of gastrointestinal side effects (e.g. nausea, vomiting and constipation) was reduced considerably with tapentadol IR.

For example, in one the study involving patients with end-stage joint disease of the hip or knee, gastrointestinal side effects for the respective doses of tapentadol IR were 29% and 40%, compared to 69% for oxycodone IR.

These side effects caused a significantly higher proportion of patients taking oxycodone IR to discontinue treatment (29%) than tapentadol IR (13% and 18% for the 50 mg and 75 mg doses respectively).

Dr Joan Hester (Consultant in Pain Medicine, King's College Hospital, London, and President of the British Pain Society) said that while opioids were still the mainstay of pain management, their widespread use was still a continuing cause for concern. They often lacked efficacy – especially in mixed pain conditions, they caused gastrointestinal and CNS side effects, and were associated with a high level of dependence.

'Are we meeting the needs of our patients?' she asked. 'In many cases we are not, and I hope that tapentadol will be among the drugs we are able to use to treat pain in the future.'

Professor Marie Fallon (Chair of Palliative Medicine, University of Edinburgh) commented that the duration of chronic pain is often a lifetime experience, with serious consequences for quality of life. Meanwhile, opioid-related side effects were often the cause of poor compliance and the reason why patients discontinued treatment.

Dr Joan Hester, Consultant in Pain Medicine, King's College Hospital, London, and President of the British Pain Society

'The pain relief derived from opioids is often unsatisfactory,' she said, 'with adverse events limiting potential analgesic benefits.'

Dr Beverley Collett (Consultant in Pain Management and Anaesthesia, Leicester Royal Infirmary) said that the expanding use of strong opioids by patients experiencing severe pain poses a significant challenge to health-care professionals, and she welcomed the introduction of new agents with the potential to minimize opioid-induced side effects.

A pan-European survey of more than 46 000 people carried out in 2006 revealed that nearly one-fifth of all adults experience moderate-to-severe chronic pain. In the UK, the figure was 17%.

'Chronic, severe pain is common and diverse – but not well understood,' commented Dr Collett, adding that although the patients in this study were fairly typical, such pain could also arise from hernia repair, hysterectomies, breast and gallbladder surgery, even coronary artery bypass surgery. Only now are doctors beginning to warn patients of the potential for long-term pain arising from these procedures.

'A quarter of all people with chronic, severe pain go on to be diagnosed with depression,' said Dr Collett. 'A quarter will lose their jobs – often leading to significant social and financial consequences, not only for the patient but his or her immediate family.'

She reported that up to 70% of people who take opioids for pain relief suffer opioid-induced bowel dysfunction. 'It's a huge problem, and not surprisingly, one of the main reasons patients discontinue pain relief therapy.'

Stephen Pinn

Palliative care 'should be' a human right

The 12th World Congress on Pain opened by calling for palliative pain relief to be made a human right.

Outgoing President Troels S Jensen of the International Association for the Study of Pain, signed an international petition calling for the move to be made during his opening address. The Joint Declaration and Statement of Commitment is a joint initiative between the International Association for Hospice and Palliative Care and the Worldwide Palliative Care Alliance.

Dr Jensen said: 'We believe that every human being should be entitled to relief from pain.'

He continued: 'To effectively meet the challenges of pain management in the 21st century, we need to encourage governments to provide researchers and physicians with the tools to make the treatment and research of pain a key priority across the globe.'