newsround

Selected reports edited by Janet Fricker

Aprepitant for managing pruritus

■ Lancet Oncology

Use of an aprepitant decreased the severity of pruritus induced by biological cancer treatments, an Italian pilot study reports.

Pruritus (itch) is a common symptom among patients taking targeted drugs, especially those targeting the EGFR pathway. Treatment of pruritus is considered important for patients' well-being, not least because untreated side-effects might contribute to poor adherence to oral anticancer treatments.

Aprepitant, an oral neurokinin-1 receptor antagonist that blocks mast-cell degranulation caused by neurokinin-1 receptor, is commonly used for prevention of acute and delayed nausea or vomiting caused by highly emetogenic chemotherapy, and for prevention of postoperative nausea and vomiting.

In 2010, Daniele Santini and colleagues, from the Bio-Medico University of Rome, Italy, reported off-label use of aprepitant for treatment of pruritus in two patients with stage 4 non-small-cell lung cancer receiving erlotinib. On the basis of finding that both patients recovered from pruritus 24 hours after administration, the team designed a pilot study to assess aprepitant in the management of pruritus caused by biological drug treatments.

Between September 2010 and November 2011, 45 patients were enrolled into the single-centre prospective study. Two different populations were studied: patients with severe itch resistant to standard treatment with steroids or antihistamines (the refractory group), and patients who had not received any treatment for severe pruritus (the naïve group).

For the refractory group, aprepitant (125 mg on day 1; 80 mg on day 3; 80 mg on day 5) was given to patients; while for the naïve group, the same schedule for aprepitant was used after the first onset of severe pruritus.

Results show that for patients refractory to standard treatment for pruritis, aprepitant reduced median itch on the visual analogue scale (VAS) from 8.00 (95%CI 7.93–8.57) at baseline to 1.00 (95%CI 0.00–2.00) after one week of treatment ($P<0.0001$). For patients previously treated for pruritis, aprepitant reduced the VAS score from 8.00 (95%CI 7.43–8.37) at baseline to 0.00 (95%CI 0.06–1.08) after one week of treatment ($P<0.0001$).

"To our knowledge, this trial is the first clinical study to show that aprepitant can help management of pruritus caused by biological treatments, both as a first choice treatment and after failure of standard treatments," write the authors.

The results, they add, support the notion that substance P activates dermal mast-cells through neurokinin receptors, inducing release of pruritogens, which causes onset of pruritus. Randomised phase II or III trials should now be undertaken to validate the efficacy of aprepitant treatment.

In an accompanying commentary Olivier Mir, from the Institut Gustave Roussy, Villejuif, France, and Romain Coriat, from Paris Descartes University, France, write, "Particular attention should be given to the risk of drug–drug pharmacokinetic interactions, since aprepitant can alter the activity of cytochrome P450 3A4 isoform (CYP3A4), an enzyme involved in the metabolism of a range of anticancer drugs."

Tyrosine kinase inhibitors metabolised by CYP3A4, they add, include erlotinib, gefitinib, sunitinib, sorafenib, imatinib, pazopanib, axitinib, and regorafenib.

■ D Santini, B Vincenzi, F Guida et al. Aprepitant for management of severe pruritus related to biological cancer treatments: a pilot study. *Lancet Oncol* October 2012, 13:1020–24

■ O Mir, R Coriat. Aprepitant for pruritus: drug–drug interactions matter. *ibid*, pp 964–965

Prostate cancer: intermittent androgen suppression non-inferior to continuous treatment

■ New England Journal of Medicine

Intermittent androgen deprivation has been found to be non-inferior to continuous therapy with respect to overall survival for men with prostate specific antigen (PSA) levels rising after initial or salvage radiotherapy. The phase III NCIC Clinical Trials Groups study, funded by the Canadian Cancer Society, also showed some quality-of-life factors improved with intermittent therapy.

The development of reversible non-oestrogenic castrating regimens, along with the availability of PSA assays, laid the foundations for the study. Preclinical studies have shown that intermittent therapy lengthens intervals from initial androgen deprivation therapy to development of hormonal resistance. The adverse effects of androgen therapy on quality of life have been well described and include sexual dysfunction, hot flushes, fatigue, anaemia, decreased bone density and muscle mass, altered blood lipid profiles, depression, cognitive dysfunction and worsening of metabolic syndrome.

Juanita Crook and colleagues, from Columbia Cancer Agency, Kelowna, Canada, investigated

the hypothesis that intermittent androgen deprivation might provide better disease control while at the same time providing relief from castration-associated adverse effects.

Between January 1999 and November 2005, 1386 men with PSA levels greater than 3 ng/ml one year after primary or salvage radiotherapy for localised prostate cancer were randomised in a 1:1 ratio to either intermittent therapy for eight months (n=690) or continuous therapy (n=696). Both groups received luteinising hormone-releasing hormone agonists combined with a non-steroidal antiandrogen. PSA levels were monitored every two months. In the intermittent group, therapy was paused only if there was no evidence of clinical disease progression and the patient's PSA levels were less than 4 ng/ml and not more than 1 ng/ml above previous recorded values.

At a median follow-up of 6.9 years, 268 patients in the intermittent therapy group had died, versus 256 in the continuous therapy group. The median overall survival was 8.8 years in the intermittent group versus 9.1 years in the continuous group. The P-value for non inferiority (HR<1.25) was 0.009, supporting the hypothesis that intermittent therapy was not inferior to continuous therapy.

In terms of adverse events, no significant differences were found between the two groups. Intermittent therapy was associated with significantly better scores for hot flushes (P<0.001), desire for sexual activity (P<0.001) and urinary symptoms (P=0.006), with a trend towards improvements in levels of fatigue (P=0.07).

Although intermittent androgen-deprivation therapy appears to provide overall quality-of-life benefits, write the authors, differences were not as "profound" as expected. "Part of the explanation for this lies in the timing of the quality-of-life assessments, which were performed at regular intervals in both treatment groups without regard to the treatment phase (on or off treatment)," write the authors.

The cost savings from reductions of drug use in the intermittent therapy group (approximately one third that of the continuous therapy group), may be partially offset by the closer follow-up required, write the authors.

In an accompanying commentary, Oliver Sartor, from Tulane University School of Medicine, New Orleans, praised the research as 'the most definitive study to date', comparing intermittent versus continuous androgen-deprivation therapy in non-metastatic cancer. He noted, however, that important questions remain unanswered, such as whether men with rising PSA levels need treatment. "This is a heterogeneous patient group, and only a minority of men might be expected to have clinical consequences from their rise in PSA level," he writes.

■ J Crook, C O'Callaghan, G Duncan et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *NEJM* 6 September 2012, 367:895–905

■ O Sartor. Androgen deprivation – continuous, intermittent or none at all? *ibid*, pp 945–946

Study provides reassurance about cognitive decline following chemotherapy

■ Journal of Clinical Oncology

Cognitive deficits in breast cancer patients treated with chemotherapy six months previously were found to be small in magnitude and limited to verbal and visuospatial ability domains, a meta-analysis has reported.

The terms 'chemofog' and 'chemobrain' are often used by patients to describe an ill-defined impairment of cognitive function following chemotherapy. But evidence is mixed, with several studies reporting deficits and others not. Although four meta-analyses have previously examined cognitive functioning in patients treated with chemotherapy, none has focused exclusively on the post-treatment period.

In the current study, Heather Jim and colleagues, from Lee Moffitt Cancer Center, Tampa, Florida, set out to conduct a meta-analysis of cognitive functioning in breast cancer survivors who had been treated with chemotherapy six months previously. The meta-analysis focused on women with breast cancer, as the vast majority of existing research has been conducted in this population. "If cognitive deficits occur during treatment but resolve thereafter, then studies including patients primarily receiving treatment may negatively influence findings," write the authors. However it is possible, they add, that deficits occurring during treatment may persist.

The meta-analysis identified 17 studies covering a total of 807 breast cancer survivors who had been treated with standard-dose chemotherapy at least six months earlier. For the studies, neuropsychological tests were categorised according to eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability.

Results showed that deficits in cognitive functioning were found in patients treated with chemotherapy relative to controls or their own pre-chemotherapy baseline in the domains of verbal ability (g=-0.19; P<0.01) and visuospatial ability (g=-0.27; P<0.01). Patients treated with chemotherapy performed worse than non-cancer controls in verbal ability and worse than patients treated without chemotherapy in visuospatial ability (both P<0.01). Age, education, time since treatment, and endocrine therapy did not moderate observed cognitive deficits in verbal ability or visuospatial ability

"Clinically, our findings suggest that patients with breast cancer considering chemotherapy be educated that >6 months after treatment, they can expect normal cognitive functioning with the exception of slight impairments in verbal abilities (e.g., word-finding difficulty) and visuospatial abilities (e.g., getting lost more easily)," write the authors.

However there is likely to be considerable variability in cognitive outcomes, they add, with some patients reporting no impairments and other reporting more severe or pervasive deficits. Patients treated with chemotherapy reporting cognitive difficulties should be referred to a neuropsychologist for evaluation and management of cognitive deficits.

In an accompanying commentary, Gary Rodin from the University of Toronto, Canada, and Tim Ahles from Memorial Sloan-Kettering Cancer Center, New York, write that most studies of cognition and cancer exclude patients with a variety

of conditions that increase vulnerability to post-treatment cognitive decline, including history of head injury, neurologic disorders, depression and learning disabilities. "Consequently, the cognitive changes reported may represent the tip of the iceberg in terms of the cognitive impact of cancer treatments," they write.

■ H Jim, K Phillips, S Chait et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *JCO* 10 October 2012, 30:3578–87

■ G Rodin, T Ahles. Accumulating evidence for the effect of chemotherapy on cognition. *ibid* pp 3568–69

Interventions reduce symptoms in breast-cancer-induced menopause

■ Journal of Clinical Oncology

Women who experience early menopause following treatment for breast cancer who undergo cognitive therapy (CBT) and physical exercise (PE) showed improvements in endocrine symptoms compared to controls who did not receive such interventions, reports a Dutch study.

It is well known that chemotherapy and endocrine therapy in patients with pre-menopausal breast cancer may result in early onset of menopause. Primary symptoms include hot flushes, night sweats and vaginal dryness, and secondary symptoms include weight gain, urinary incontinence and psychological distress.

With growing evidence that cognitive behavioural therapy and physical exercise can have a positive impact on vasomotor symptoms in naturally occurring menopause, Neil Aaronson and colleagues, from the Netherlands Cancer Institute in Amsterdam, set out to explore whether such benefits could also be achieved in breast cancer patients experiencing treatment-induced menopause.

In the study, 422 women with primary breast cancer aged less than 50 years were randomly assigned, between January 2008 and December 2009, to CBT (n=109), PE (n=104), CBT and PE (n=106) or to a waiting-list control group (n=103). Self-report questionnaires were completed at baseline, 12 weeks, and six months. The CBT programme consisted of six weekly group sessions of 90 minutes each, including relaxation exercises; while the PE programme was a 12-week individually tailored home-based programme for 2.5–3 hours per week, where physiotherapists assisted the women in selecting an appropriate form of exercise, from swimming, running and cycling.

Results showed that, in comparison with patients in the control group, those in the intervention groups had significant decreases in levels of endocrine symptoms, measured using the Functional Assessment of Cancer Therapy (P<0.001; effect size 0.31–0.52). Urinary symptoms, measured using the Bristol Female Lower Urinary Tract Symptoms Questionnaire were also decreased (P=0.002; effect size 0.29–0.33). Furthermore, the active groups showed improvements in physical functioning measured using the physical functioning subscale of the 36-Item Short Form Health Survey (P=0.002; effect size 0.37–0.46).

PE, the researchers note, "affects primarily the frequency with which endocrine symptoms are experienced, but not the frequency of hot flashes and night sweats specifically," while CBT, in contrast, "seems to not only affect symptom frequency, but also the perceived burden of hot flashes and night sweats."

"In conclusion, our findings indicate that both CBT and PE can have salutary effects on menopausal symptoms and to a lesser degree on sexuality and HRQoL-related functioning among patients with breast cancer experiencing treatment-induced menopause," write the authors.

The results, they add, tend to support the hypothesis that cognitive and emotional factors can modify the experience of menopausal symptoms, whereas stress reduction techniques and physical exercise may have a more direct effect on menopausal symptoms via the thermoregulatory system and an improvement in overall physical condition. "Future work is needed to improve the design and the planning of these interventions, with an eye toward improving program adherence," write the authors.

In an accompanying commentary, Debra Barton and Charles Loprinzi, from the Mayo Clinic, Rochester, Minnesota, write, "Although the trial... provides helpful information, much more work needs to be completed to best understand the ideal way to clinically apply non-pharmacologic therapies for the treatment of hot flashes, night sweats, and other estrogen deficiency symptoms."

■ S Duijts, M van Beurden, H Oldenburg. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *JCO* 20 November 2012, 30:4124–33

■ D Barton, C Loprinzi. Using one's head to treat menopausal symptoms. *ibid*, pp 4059–60

Acupuncture relieves symptoms of xerostomia

■ Annals of Oncology

Patients with head and neck cancers randomised to acupuncture were twice as likely to report improved symptoms of xerostomia as patients receiving oral care sessions, the UK ARIX study has found. No significant differences were found in saliva production between the two groups, however.

Patients who have received radiotherapy for head and neck cancer often suffer from the unpleasant and distressing side effect of dry mouth (xerostomia) caused by damage to the salivary glands from radiation. Chronic xerostomia impairs quality of life, interfering with taste, chewing, swallowing, speaking and sleeping. Management options providing short-term help include mouth washes, gels and toothpastes. While the drug pilocarine can offer relief, the side-effects of muscarinic receptor stimulation can cause the unpleasant symptoms of sweating, rhinitis and urinary frequency. Studies have suggested that acupuncture, an increasingly accepted method for controlling pain,

chemotherapy-induced nausea and hot flushes, might also relieve symptoms of xerostomia.

In the ARIX (Acupuncture in the treatment of Radiation-Induced Xerostomia) trial, investigators led by Val Jenkins, from the Brighton and Sussex Medical School, UK, investigated the efficacy of acupuncture in ameliorating patients' self-reported symptoms of dry mouth.

For the study ,145 patients with chronic radiation-induced xerostomia lasting longer than 18 months were randomised to receive group acupuncture sessions for 20 minutes every week for eight weeks (*n*=70), or two oral care educational sessions for one hour, one month apart (*n*=75). Then four weeks after the end of the two different types of care, patients swopped over to receive the other treatment. Patients were recruited from seven cancer centres in the UK.

Patients answered the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQC30), and the Head and Neck subscale. Saliva production was measured using Schirmer strips, both in the stimulated situation (where lemon juice was applied to the tongue) and non-stimulated situation.

Results showed that, in comparison with oral care, acupuncture produced significant reductions in patient reports of severe dry mouth (OR=2.01; *P*=0.031), sticky saliva (OR=1.67; *P*=0.048), needing to sip fluid to swallow food (OR=2.08; *P*=0.011) and in waking up at night to drink (OR=1.71; *P*=0.013). There were no significant changes in either stimulated or unstimulated saliva measurements over time.

"The trial appears to establish the effectiveness of the technique, and group sessions offer a pragmatic and affordable system of delivering the intervention," write the authors.

Future studies, add the authors, may be warranted to refine the technique further, establish the duration of benefit and length of treatment, and whether booster sessions might improve and maintain efficacy.

The mechanisms underpinning the benefits of acupuncture are not clear. "Acupuncture may produce autonomic stimulation of any residual salivary gland tissue directly or by increasing blood supply to it or the multiple minor salivary glands that line the upper aerodigestive tract," suggest the authors.

■ R Simcock, L Fallowfield, K Monson et al. ARIX: a randomised trial of acupuncture v oral care sessions in patients with chronic xerostomia following treatment of head and neck cancer. *Ann Oncol*, published online 25 October 2012, doi:10.1093/annonc/mds515

Asymptomatic VTEs associated with increased risk of death in cancer patients

■ **British Journal of Cancer**

Asymptomatic venous thrombotic events (VTEs) of the lower limbs in ambulatory cancer patients were found to be associated with a 2.4-fold increased risk for death during nine months follow-up despite anticoagulation medications.

VTEs are a common complication associated with malignancy, with increased microparticle tissue factor activity described in cancer patients with VTE, in addition to increases in circulating tumour cells and high platelet counts. In a recent study, symptomatic and asymptomatic VTEs were found to occur in more than one third of pancreatic cancer patients.

In the current prospective cohort study, Thomas Gary and colleagues, from the Medical University Graz, Austria, evaluated the occurrence of VTEs of the lower limbs in 150 consecutive ambulatory cancer patients seen at their outpatient clinic. The team explored the association with survival during nine months of follow-up. To evaluate the occurrence of VTEs, compression ultrasound (CUS) was performed by two experienced vascular specialists in all patients at baseline, with venous thrombosis in the pelvic veins examined by duplex Doppler sonography of the common femoral vein performed after a Valsalva manoeuvre.

Results show that the most frequently included tumour entities were colorectal and anal cancer (32.7%), breast (22.7%), pancreatic (21.3%), lung (4.7%), gastro-oesophageal (4.7%) and prostate (3.3%). Chemotherapy was being used by 82.7% of patients in the study.

Altogether asymptomatic VTEs were identified in 27 patients (18%), with 13 asymptomatic SVT (superficial venous thrombotic) events in the saphenous system and 16 asymptomatic DVT (deep venous thrombotic) events – two patients had both a SVT and DVT event. In the nine-month follow-up period, 9 out of 27 patients with asymptomatic VTEs at baseline died, compared with 14 out of 123 patients without VTEs at baseline (*P*=0.001). Even after adjustment for age, sex, stage of cancer, tumour entity, chemotherapy, surgery and radiotherapy, an asymptomatic VTE of the lower limbs was associated with a 2.4-fold increased risk for death (HR 2.4, 95%CI 1.2–5.3; *P*=0.03).

In patients with asymptomatic VTEs, the main tumour entities were pancreatic cancer (29.6%), colorectal and anal cancer (25.9%), and breast cancer (18.5%). Chemotherapy was applied in 88.9% of these patients.

"Our study shows for the first time in a prospective manner that ambulatory cancer patients are at high risk to suffer a completely asymptomatic VTE of the lower limbs. These patients are at higher risk to die in the following 9 months," write the authors.

Most interesting, they add, was the finding that death occurred despite low-molecular-weight heparin therapy, making a fatal pulmonary embolism (PE) as a reason for death in these patients unlikely. "We therefore hypothesise that the occurrence of an asymptomatic VTE seems to be an expression of an advanced stage or associated with a more aggressive biologic behaviour of the malignant disease," they write. The aetiology of these completely asymptomatic VTEs requires further investigation.

Limitations of the study include small sample sizes and the fact that only one compression ultrasound was performed at baseline. There is a need for larger prospective studies, add the authors, powered to detect differences in short-term survival between superficial, distal and proximal deep venous thrombosis.

■ T Gary, K Belaj, K Steidl et al. Asymptomatic deep vein thrombosis and superficial vein thrombosis in ambulatory cancer patients: impact on short term survival. *Br J Cancer* 9 October 2012, 107:1244–48