NEWSROUND

Selected reports edited by Janet Fricker

Intervention by nurses can help combat depression in cancer patients

→ The Lancet

A team of Scottish researchers has shown that cancer patients offered a depression care intervention, delivered by specially trained oncology nurses with no previous psychiatric experience, showed improvements in symptoms of depression compared to patients offered usual care. The beneficial effects of the "depression care for people with cancer" package (DCPC) were found to be sustained at 12 months' follow-up, to the surprise of the investigators.

Michael Sharpe and colleagues, from the University of Edinburgh Cancer Research Centre, Western General Hospital, Edinburgh, Scotland, undertook the SMaRT (Symptoms Management Research Trials) oncology 1 trial to study the use of the DCPC package, which had been originally designed for the treatment of depression in primary care.

In the study, funded by Cancer Research UK, 200 patients – all with a cancer prognosis of more than six months (to ensure they could complete the trial) and major depression – were randomised to receive the usual care of antidepressants and mental health referrals or usual care in addition to the DCPC programme. Patients allocated to the DCPC arm were offered an average of seven one-to-one consultations over three months with a specially trained cancer nurse. The sessions aimed to help patients to understand depression and its treatments, including antidepressants, and provided problem-solving strategies to help patients overcome feelings of helplessness. The nurses also communicated with each patient's oncologist and primary care doctor about the management of their depression.

Following the initial treatment, the nurse monitored the patient's progress by telephone and provided optional booster sessions if needed. Depression levels were measured using the self-reported Symptom Checklist-20 depression scale (range 0–4), and also by interview at three, six, and 12 months for both groups.

The nurses, who had no previous experience of psychiatry, were trained to deliver the intervention using written materials, tutorials and supervised practice over a period of at least three months.

Sharpe and colleagues found that patients who received DCPC had a lower depression level – by 0.34 on the five-point scale – than those who did not receive DCPC. The treatment group also had a major depression rate that was 23% lower than in the usual care group. After 12 months, the benefits from the DCPC intervention were still evident. The DCPC intervention also improved anxiety and fatigue, but did not improve pain or physical functioning.

In future studies, the team hopes to investigate whether the programme is cost-effective if implemented on a larger scale, and whether the intervention might also benefit patients who have cancers with a poor prognosis, such as lung cancer.

In an accompanying comment, Gary Rodin (Princess Margaret Hospital, University Health Network, Toronto, Canada), wrote: "In a well-designed study, Sharpe and colleagues have shown that trained nurses with no previous psychiatric experience can deliver a cost effective collaborative psychosocial intervention for cancer patients with major depressive disorder. Such multi-component interventions are potentially feasible in cancer treatment centres and can be perceived by patients as less stigmatising than referral to a mental health specialist."

■ V Strong, R Waters, C Hibberd et al. Management of depression for people with cancer (SmaRT oncology 1): a randomised trial. *Lancet* 5 July 2008, 372:40–48

Treatment of depression in patients with cancer. Comment. G Rodin *ibid* pp 8–10

Multiple myeloma: bortezomib increases time to progression

→ N Engl J Med

Adding bortezomib to combination therapy with melphalan and prednisone in newly diagnosed multiple myeloma patients who are

not eligible for high-dose chemotherapy, increased time to progression, a phase III study has found.

For over 40 years the standard of care for newly diagnosed multiple myeloma patients who are not candidates for high-dose chemotherapy has been combination treatment with melphalan and prednisone. More recently, high-dose therapy with haematopoietic stem-cell transplantation has become the preferred treatment for patients less than 65 years, but older patients generally do not tolerate such an approach, which rules this option out for most patients since the median age at diagnosis is approximately 70 years. Jesus San Miguel and colleagues from Hospital Universitario de Salamanca, in Spain, therefore set out to investigate the benefits of adding the protease inhibitor bortezomib to the melphalan and prednisone.

The investigators randomly assigned 682 patients (ineligible for high-dose therapy) to receive nine six-week cycles of melphalan (9 mg/m^2 body-surface area) and prednisone (60 mg/m^2) on days 1 to 4, either alone (for the control group) or with bortezomib (1.3 mg/m^2) on days 1, 4, 8, 11, 22, 25, 29 and 32 during cycles 1 to 4, and on days 1,8, 22, and 29 during cycles 5 to 9. Results show time to disease progression among patients receiving bortezomib in addition to melphalan-prednisone was 24.0 months, compared to 16.6 months for the control group (HR 0.48; P<0.001). There were also significant improvements associated with bortezomib therapy for the rate of complete response, time to subsequent myeloma therapy and overall survival.

Grade 3 adverse events were more frequent in the bortezomib group (53% vs 44%, P=0.02), but no significant differences in grade 4 events were found.

Superior efficacy in the treatment of myeloma, say the authors, has now been shown with both bortezomib and thalidomide. "Melphalan and prednisone alone can no longer be considered the standard of care in patients who are 65 years of age or older," they conclude.

■ Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. JF San Miguel, R Schlag, NK Khuageva et al. *N Engl J Med* 28 August 2008, 359:906–917

Pegylated interferon delays recurrence of melanoma

➜ The Lancet

Administration of pegylated interferon alfa-2b significantly improves recurrence-free survival in patients with resected stage III (lymph-node metastatic) cutaneous melanoma in comparison to observation alone, according to a study by the EORTC. No difference, however, was found in overall survival.

Although adjuvant therapy with interferon alfa is widely used for melanoma patients with stage IIb and stage III melanoma, who are at high risk of recurrence after definitive surgery, controversy remains over whether it is effective enough to justify routine use, given the toxicity of the treatment.

The phase III study (EORTC 18991) principal investigator, Alexander Eggermont (Erasmus University Medical Centre, Rotterdam, Netherlands), set out to investigate whether using pegylated interferon could facilitate prolonged exposure while maintaining tolerability.

Patients with resected stage III melanoma were randomly assigned to receive pegylated interferon alfa-2b (n=627) or observation (n=629). Patients were started on induction doses of 6 µg/kg per week for eight weeks, then moved on to maintenance doses of 3 µg/kg per week for an intended duration of five years. Participants were assessed for recurrence and distant metastases every three months during the first three years, then every six months. After a median 3.8 years of follow-up, 328 recurrence events occurred in the pegylated interferon group compared with 368 in the observation group (HR 0.82, 95% CI 0.71-0.96; P=0.01). Distant-metastasis-free survival was longer in the interferon group than in the observation group, although this difference was not statistically significant. There was no difference in overall survival between the two groups.

The benefits were greater for patients with a less heavy disease burden. Among patients with microscopic nodal disease, there were fewer recurrences or deaths in the interferon group than in the observation group (P=0.016); but among patients with palpable nodal disease, similar numbers of recurrences (P=0.119), distant metastases (P=0.53) and overall survival (P=0.91) were seen in the two groups.

In patients with microscopic disease who had an ulceration in the primary tumour (n=186), pegylated interferon seemed to reduce the risk of recurrence, distant metastasis and death, regardless of how many nodes were involved.

Grade 3 adverse events occurred in 246 patients (40%) in the interferon group and 60 (10%) in the observation group, while grade 4 adverse events occurred in 32 patients (5%) in the interferon group and 14 (2%) in the observation group. The most commonly observed side-effects were fatigue and depression.

"Our data suggest that pegylated interferon alfa-2b could be an option for adjuvant treatment of patients with resected high-risk melanoma, especially those with lower nodal tumour burden," write the authors. "Markers of patients likely to respond to interferon are clearly needed, and this trial indicates that the combination of low tumour volume and an ulcerated primary tumour might be such a marker."

■ Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. AMM Eggermont, S Suciu, M Santinami et al. *Lancet* 12 July 2008, 372:117–126

Post-mastectomy pain defined

➜ British Journal of Cancer

Nearly one quarter of women undergoing breast cancer surgery experience post-mastectomy pain syndrome (PMPS) one and a half years after their operation, according to a recent Danish study. The results showed that pain was more likely in women undergoing early surgery, those with tumours located in the upper lateral quarter and those who were young at the time of surgery.

PMPS, often located in the axilla, the shoulder, the arm or the chest wall, is frequently

described as a "typical neuropathic pain consisting of burning pain, shooting pain, pain evoked by pressure and deep blunt pain". In the current study, OJ Vilhom and colleagues from the department of Neurology, Odense University Hospital (Denmark) set out to estimate the current prevalence of PMPS and to identify risk factors. Questionnaires were mailed to 258 women, one and a half years after they had undergone surgery for breast cancer (either mastectomy or lumpectomy) at Odense University Hospital, with similar questionnaires being sent to a reference group of 774 women.

For the purposes of the study, PMPS was defined as pain located in the area of the surgery or ipsilateral arm that was present for at least four days per week, with an average intensity of at least 3 on a numeric scale from 0 to 10.

Results show that the prevalence of PMPS was 23.9% for breast cancer surgery patients compared to 10% for the reference population (OR 2.88; 95% CI 1.84–4.51).

Three risk factors were identified as significant for PMPS – having undergone breast surgery early (OR 8.12), tumour location in the upper lateral quarter (OR 6.48) and a young age at surgery (OR 1.04). Chemotherapy, axillary dissection, mastectomy, smoking, tumour size and radiation therapy were not associated with PMPS.

Although no differences in the description of pain were found between breast cancer patients and the reference group, the location of the pain differed, with breast cancer patients more likely to experience pain in the shoulder, the area of the scar, and in more than one location.

The majority of breast cancer patients with severe pain had pain located in the shoulder, axilla or arm. "This adds evidence to the finding of tumour located in the upper lateral quarter being an important risk factor, as operation in this area may tend to cause more nerve damage than surgery in other areas of the breast," write the authors.

"Although recent advances in diagnostic and surgical procedures have reduced the frequency of the more invasive surgical procedures, there is still a considerable risk of developing PMPS after treatment for breast cancer, and development of preventive measures as well as treatments of the syndrome are highly relevant," conclude the authors.

■ The post-mastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. OJ Vilholm, S Cold, L Rasmussen et al. *Br J Cancer* 12 August 2008, 99:604–610

Bisphosphonate prevents bone loss in pre-menopausal breast cancer

➜ Lancet Oncology

Using the bisphosphonate zoledronic acid in combination with adjuvant therapy (GnRH analogues and selective oestrogen receptor modulators) in premenopausal women following surgery for early breast cancer prevents bone loss, a sub-study analysis from the Austrian Breast and Colorectal Cancer Study Group trial 12 has concluded.

The ABCSG-12 study, by Michael Gnant, from the University of Vienna (Austria) and colleagues, aimed to compare tamoxifen versus anastrozole (an aromatase inhibitor) when added to goserelin-induced ovarian suppression as an adjuvant therapy in pre-menopausal, hormone-responsive early breast cancer.

A sub-study investigated the effects on bone mineral density (BMD) in both treatment arms, as well as the protective effect of concomitant bisphosphonate zoledronic acid.

In the study, 404 patients were randomly assigned to endocrine therapy alone (goserelin and anastrozole, or goserelin and tamoxifen, n=199) or to endocrine therapy concurrent with zoledronic acid (n=205). Zoledronic acid was delivered by seven intravenous infusions spaced over the three-year duration of the study. Lumbar spine and trochanter BMD measurements were made at baseline, 36 months and 60 months.

Results show after 36 months, the endocrine therapy alone arm had significant loss of BMD in comparison to baseline measurements at the lumbar spine (-11.3%, mean difference -0.119 g/cm^2; P<0.0001) and at the trochanter (-7.3%, mean difference -0.053 g/cm^2; P<0.0001). Patients who received zoledronic acid had stable BMD at 36 months, (+0.4%, mean difference 0.0004 g/cm^2 at the lumbar spine and +0.8%, mean difference 0.0006 g/cm^2 at the trochanter).

At 60 months (24 months after study completion), patients not receiving zoledronic acid still had decreased BMD at both sites compared with baseline (lumbar spine P=0.001, trochanter P=0.058) , while those receiving zoledronic acid still had increased BMD at both sites (lumbar spine P=0.02; trochanter P=0.07).

In the group randomised to no zoledronic acid, patients on anastrozole experienced greater BMD loss than those on tamoxifen at 36 months in the lumbar spine (P<0.0001).

Zoledronic acid combined with goserelin plus tamoxifen or anastrozole was generally well tolerated, with the only significant adverse events being bone pain (P=0.003), arthralgia (P=0.013) and fever (P=0.0001).

"Bone loss associated with adjuvant endocrine therapy in premenopausal women with early-stage breast cancer is of substantial clinical concern, because these women typically survive for many years after treatment," write the authors, adding that it will be interesting to monitor the long-term proportion of fractures, to establish whether substantial fracture prevention is associated with zoledronic acid therapy.

■ Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone mineral density substudy. M Gnant, B Mlineritsch, G Luschin-Ebengreuth et al. *Lancet Oncology* September 2008, 9:840–849

Promoting adherence to long-term hormonal therapy in breast cancer

➜ British Journal of Cancer

Women treated with long-term hormonal (endocrine) therapy are more likely to stick with the treatment if they are looked after in specialised oncology units than if they are

cared for by a family doctor, according to a major follow-up study.

Hormonal therapy has been recommended for the vast majority of postmenopausal women with hormone-receptor-positive breast cancer since the late 1990s. Expert guidelines recommend that elderly women with hormone-receptor-positive breast cancer take tamoxifen for five years. However, there are lots of reasons why it can be difficult for women to take hormonal therapy for such a long time. Previous research evaluating the use of adjuvant hormone therapy among post-menopausal breast cancer patients showed that between 15% and 50% women did not adhere to the treatment as recommended, with some women refusing even to start the treatment.

In the new study, a group of researchers from Basel, Switzerland, studied an unselected group of 325 postmenopausal women who were diagnosed with hormone-receptor-positive invasive breast cancer. They looked carefully at the different clinical situations that led to the women stopping their hormonal treatment, or not taking it exactly as recommended. Results showed that only 191 of the 287 patients (66.6%) who started hormonal therapy for five years completed this treatment.

Thirty-one patients (10.8%) chose independently to stop their hormonal therapy before the end of the recommended five years. The main reasons for non-adherence were general discomfort (29.0%), hot flushes (12.9%), skin symptoms and hair loss (9.7%), visual disturbance (3.2%) and alcohol dependency or psychiatric illness (9.7%). Just over one-third of these women did not give a reason for stopping their treatment. A further 8.9% of the women refused the recommended endocrine therapy after extensive counselling and never even began this treatment.

In the study, 25 patients changed their hormonal medication due to therapy-related adverse effects. Of these, 20 women (80%) completed their therapy after changing the drug they were prescribed.

Patients who had their follow-up care with a general practitioner were significantly more likely to be non-adherent than those looked after in an oncology unit (P=0.0088). Only one in ten (10.8%) of the women cared for by a specialised oncology unit did not take their hormonal therapy as recommended. The researchers concluded, "Our data show that, when compared with other studies, low non-adherence rates can be realistically achieved." They noted that this was probably associated with the fact that practitioners in specialist oncology units had received targeted education in patient-centred communication. "An important aspect of non-adherence is the ability of the physician to intervene and change the attitude that led to discontinuation."

■ Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer. U Güth, DJ Huang, A Schötzau et al. *Br J Cancer* 29 July 2008, 99:428–433

Higher radiation levels show benefit in prostate cancer

➔ Int J Radiat Oncol Biol Phys

For prostate cancer, higher radiation dose levels are associated with significant improvements in long-term biochemical tumour control outcomes and reduction in the development of distant metastases, a US study has found.

Several randomised studies have already shown improved prostate-specific antigen (PSA) relapse-free survival outcomes for patients with favourable-, intermediate- and high-risk features who are treated with high doses of radiation in comparison to low doses.

In an earlier publication, Michael Zelefsky and colleagues from Memorial Sloan-Kettering Cancer Center (New York), reported improved biochemical outcomes when dose levels of 75 Gy and higher were used with three-dimensional conformal radiotherapy (3D-CRT). The current report presents a median follow-up of 6.6 years (range 3–18 years) of the same study.

A total of 2,047 patients with localised prostate cancer were treated with 3D-CRT or intensity-modulated radiotherapy (IMRT), with prescribed dose levels ranging from 66 to 86.4 Gy. Prior to radiotherapy, 990 patients (48%) were treated with short-course (three-month) androgen deprivation therapy (ADT) to decrease the size of their enlarged prostate prior to radiotherapy. Follow-up evaluations were performed at intervals of three to six months for five years, then yearly thereafter. Patients were classified into recurrence risk groups according to the National Comprehensive Cancer Network guidelines.

Results show that, for patients deemed to be at intermediate risk of recurrence, radiation dose was an important predictor for improved PSA relapse-free survival (P<0.0001), and improved distant-metastases-free survival (P=0.04). The beneficial effect was found to be most apparent between those receiving 75.6 Gy and more, compared with 70.2 Gy or less. Other variables, such as neoadjuvant ADT and age, were not significant predictors of biochemical control.

Higher dose levels were associated with improved biochemical outcomes in high-risk patients as well. Five-year PSA relapse-free survival outcomes for patients who received 86.4, 81, 75.6 and 70.2 Gy or less were 71%, 66%, 61% and 40% respectively.

"Taken together with other data, our findings confirm the underlying hypotheses and rationale for dose escalation in patients treated with clinically localised prostate cancer; namely that higher radiation doses improve local tumor control within the prostate, which in turn reduces the risk of distant metastases," write the authors.

The use of ADT was found to be a significant variable for improved biochemical control rates in high-risk patients, but not in intermediate-risk patients.

"It is possible that longer courses of ADT may further improve outcomes and reduce cancer-related deaths, even in the setting of higher radiation doses," write the authors, adding that only randomised trials will be able reliably to ascertain the role of hormonal therapy for patients receiving high-dose external beam radiotherapy.

■ Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. MJ Zelefsky, Y Yamada, Z Fuks et al. *Int J Radiat Oncol Biol Phys* 15 July 2008, 71:1028–1033