Boost to management of rapid breakthrough cancer pain from new drug delivery technology

Abstral is an new treatment option for inadequately controlled breakthrough cancer pain in opioid-tolerant cancer patients. Abstral's formulation delivers fentanyl in a fast-dissolving sublingual tablet. It provides rapid relief of breakthrough cancer pain from 10 minutes, provides predictable dosing and is convenient and easy to use.

Breakthrough cancer pain is a transitory exacerbation of pain experienced by patients who have relatively stable and adequately controlled background pain and affects 40–80% of patients. Breakthrough cancer pain strikes very quickly and without warning in many cases, peaking in as little as 3 minutes and lasting on average for 30 minutes.

Untreated breakthrough cancer pain can significantly reduce quality of life for patients, increasing functional impairment, depression, anxiety and psychological distress, and is associated with increased use of health-care resources and medical costs.

Fentanyl is a 'fast-in, fast-out' drug. Abstral has pharmacokinetics that match the profile of breakthrough pain. Formulated as rapidly disintegrating muco-adhesive sublingual tablets, Abstral is highly lipophillic with fentanyl dissolving almost instantly from the tablets. It is highly potent, crossing the blood–brain barrier rapidly in both directions, avoiding first-pass metabolism by liver enzymes, and offering approximately 70% bioavailability.

Abstral is convenient and easy to use, dissolving under the tongue within seconds. Abstral's innovative technology means it requires less than 1 ml of fluid to dissolve.

'Breakthrough cancer pain is a common problem, which despite being self-limiting has significant physical, psychological, social and economic consequences,' said Dr G Zeppetella, Consultant in Palliative Medicine and Medical Director, St Clare Hospice, Essex.

'The relatively fast onset and short duration of most breakthrough pain makes its management with oral opioids far from ideal. The development of transmucosal opioid formulations that are safe and effective, and provide pain relief in a time frame consistent with the rapid time course of most breakthrough pain, is an exciting prospect,' he concluded.

Valproate gives higher risk of autistic children

Vital information about pregnancy and antiepileptic drugs is unlikely to reach thousands of women with epilepsy, warns Epilepsy Action. The charity fears that this is putting mothers and unborn children at unnecessary risk.

A study published in *Neurology* concluded that there is a link between the antiepileptic drug sodium valproate and having children with autistic spectrum disorder (Bromley et al, 2008). According to the study, women taking sodium valproate face a seven times greater risk of having a child with autistic spectrum disorder than women without epilepsy.

Epilepsy Action welcomes these findings but worries that such vital information is unlikely to reach women with epilepsy.

A survey carried out by the charity in 2007 revealed that 25% of women with epilepsy who were pregnant or had given birth in the previous 5 years did not receive any preconception counselling. Also, 68% had not been offered joint care by an epilepsy specialist nurse and midwife. This is despite clear guidelines from the National Institute for Health and Clinical Excellence on the management of epilepsy.

The charity also fears that many health professionals responsible for the care of women with epilepsy – obstetricians, midwives, health visitors, and GPs – are still not aware of these issues.

Around 5000 women with epilepsy become pregnant every the year in the UK. The majority of women will experience uncomplicated pregnancies and give birth to healthy babies.

The aim in epilepsy care is that women achieve good seizure control while posing the minimum risk to the unborn child. Women should never stop taking epilepsy medication without consulting their GP and epilepsy specialist as this could be potentially harmful to their health and their unborn child.

Bromley RL, Mawer G, Clayton-Smith J, Baker GA; Liverpool and Manchester Neurodevelopment Group (2008) Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* **71**(23): 1923–4

Atazanavir approved for treatment-naïve HIV-1-infected adults

The Scottish Medicines Consortium has approved the once-daily protease inhibitor Reyataz (atazanavir) for use within NHS Scotland in antiretroviral treatment-naïve human immunodeficiency virus (HIV-1) infected adults, in combination with other antiretroviral medicinal products. This is an extension of previous guidance issued in 2004 approving atazanavir for use in HIV-1 infected, antiretroviral treatment-experienced adults, in combination with other antiretroviral medicinal products in those patients who do not require concomitant statin use.

'The Scottish Medicines Consortium's decision to extend the use of atazanavir, in combination with other antiretrovirals, to treatment-naive HIV-1 adults is positive news, especially for those newly diagnosed with HIV,' commented Dr Clifford Leen, Consultant, Infectious Diseases, Western General Hospital, Edinburgh.

'Patients will have the added benefits of receiving a treatment where there is a lower incidence of nausea and diarrhoea, and less of a lipid rise, compared to those on lopinavir. Additionally, as atazanavir is a once-daily pill, it will be more convenient, particularly as many patients are on other medications.'

Rectal artesunate could halve malaria death rate

Rectal artesunate could halve the rate of malaria death and permanent disability in remote rural areas of Africa and Asia.

Artesunate is an anti-malaria drug, usually taken as a pill or injected, which quickly kills malaria parasites. However, a suppository version has been developed for situations where neither oral treatment nor injections are options. It is intended as an emergency measure to prevent patients from dying before they are able to access adequate health care.

Most malaria deaths are of young children in rural areas. In severe cases, patients are unable to swallow oral medication, and many also live far from any hospitals or clinics where they can receive definitive treatment by injection.

A study, led by Dr Melba Gomes of the World Health Organization, examined the effects of rectal artesunate on patients with acute malaria in Bangladesh, Ghana and Tanzania.

The study took place in 291 rural villages across the three countries, and 17 826 people with suspected malaria took part, aged from 6 months to adult. Patients were randomly allocated either an artesunate suppository or a placebo. A total of 8954 were given artesunate and 8872 placebo. Most had a drop of blood taken for analysis, and 4648 samples were found to have no malaria parasites present. These patients were discounted.

The results showed no significant difference in death or permanent disability rates of remaining patients who were able to reach a clinic for injections within 6 hours.

However, many patients were unable to reach a clinic within 6 hours, and half of these had still not arrived after 15 hours. Among these patients, there were dramatic improvements and rectal artesunate was shown to halve the risk of death or permanent disability. Of the 1566 artesunate patients without further treatment after 6 hours, 29 died or were permanently disabled, *vs* 57 out of 1519 given placebo.

Gomes M, Faiz M, Gyapong J et al for the Study 13 Research Group (2008) Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet* Dec 5 [Epub ahead of print]

Strontium ranelate significantly improves bone structure in postmenopausal women

The osteoporosis treatment strontium ranelate (Protelos) significantly improved bone structure in postmenopausal women compared to the bisphosphonate alendronate, according to an oral communication of the results of the first head-to-head study of the two drugs (Rizzoli et al, 2009).

The study, which used a new, non-invasive technique called high-resolution computerized tomography, showed that strontium ranelate increased cortical bone thickness, bone volume and trabecular bone density to a significantly greater extent than alendronate over a 1-year period, a result of the different mechanisms of action of the two anti-osteoporotic agents.

Whereas alendronate only inhibits the resorption of bone, strontium ranelate has an innovative dual mechanism of action. Unlike bisphosphonates and other osteoporosis treatments, strontium ranelate simultaneously increases bone formation and decreases bone resorption, rebalancing bone turnover in favour of the formation of new and stronger bone.

The 2-year double-blind study included 88 women over the age of 50 years with postmenopausal osteoporosis who were randomized to treatment with either strontium ranelate 2 g daily or alendronate 70 mg per week. The 1-year interim results on bone microstructure, a determinant of bone strength, showed a significant +5.3% increase in cortical thickness, and a significant +2.0% increase in bone volume in the strontium ranelate-treated group, whereas there was no change in the alendronate-treated group.

'These results are highly interesting and important news for osteoporosis patients', pointed out Professor René Rizzoli, the principal investigator from Geneva University Hospital, Switzerland. 'Cortical thickness is an important determinant of the strength of long bones and in the prevention of hip fractures. Bone volume and trabecular thickness relate more closely to trabecular bone, the type of bone found in the vertebra. Our study suggests that with strontium ranelate bone may be as good if not superior as alendronate in women with postmenopausal osteoporosis.'

Rizzoli R, Felsenberg D, Laroche M et al (2009) Oral Communication 37: Strontium ranelate has a more positive influence than alendronate on distal tibia cortical and trabecular bone microstructure in women with postmenopausal osteoporosis. *Osteoporos Int* **20**: 163–86

Secondary stroke prevention

New guidance from the Scottish Intercollegiate Guidelines Network places clopidogrel as a monotherapy alternative to the combination of aspirin and dipyridamole in the secondary prevention of vascular events.

Lowering lipids with or without statins

Phase III study results show that Tredaptive 2 g (nicotinic acid/laropiprant), a new lipid-modifying therapy for patients with dyslipidaemia and primary hypercholesterolaemia, produced a significant 18% reduction from baseline in low-density lipoprotein cholesterol, a 20% increase in high density lipoprotein cholesterol and a 26% reduction in triglycerides compared to placebo. The lipid-modifying efficacy was similar when administered alone or added to ongoing statin therapy for each lipid parameter.

Reducing clots in Scotland

The Scottish Medicines Consortium has accepted Xarelto (rivaroxaban) for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery within NHS Scotland.

SAN ANTONIO BREAST CANCER SYMPOSIUM
SAN ANTONIO, TEXAS, 11–14 DECEMBER

Upfront adjuvant exemestane shows benefit over tamoxifen

Women with early breast cancer, treated with adjuvant exemestane therapy after surgery and other primary chemotherapy and/or radiotherapy, experience significantly fewer breast cancer recurrences and a longer time to the occurrence of distant metastases than women initially treated with 2–3 years of tamoxifen before receiving exemestane. These were the statistically significant interim findings of the TEAM (Tamoxifen Exemestane Adjuvant Multicenter) trial reported at the San Antonio Breast Cancer Symposium.

TEAM, which includes almost 10 000 postmenopausal women with surgically-resected invasive hormone-receptor-positive early breast cancer from nine countries, is the largest ever prospective randomized trial comparing 5 years' adjuvant therapy with an aromatase inhibitor against 2–3 years of tamoxifen followed by the same aromatase inhibitor.

The open label trial was designed in 2001 to compare 5 years' adjuvant exemestane against 5 years' tamoxifen therapy but was modified in 2004 to compare exemestane with sequential tamoxifen and exemestane following results of the Intergroup Exemestane Study. This showed a survival advantage for women who switched from tamoxifen to exemestane after 2–3 years.

Results of a first planned analysis of 9775 patients in TEAM at 2.75 years were presented by Dr Steve Jones, Medical Director of US Oncology Research, Dallas, Texas. 'A growing issue in trials of tamoxifen and aromatase inhibitors is non-compliance,' Dr Jones commented. 'Some 29% of women randomized to initial tamoxifen discontinued treatment before 2.75 years, 508 more than the number who discontinued exemestane, and this affected the outcome.'

The intention-to-treat analysis showed an 11% relative risk reduction (hazard ratio=0.89) in disease-free survival favouring exemestane (P=0.12). When women not taking study drugs as per protocol were excluded, relative risk reduction increased to a significant 17% (P=0.02). 'Disease-free survival takes account of all deaths and clinical events other than breast-related ones so can signal if a drug shows evidence of unforeseen harm. We saw none,' Dr Jones added.

'Both these drugs are very effective at preventing cancer recurrence so by 2.75 years we had seen only 570 breast cancer events among almost 10 000 women,' he noted.

Relapse-free survival showed a 15% relative risk reduction favouring exemestane on the intention-to-treat analysis (P=0.05) and time to distant metastases showed a 19% risk reduction (P=0.03).

The most common adverse symptoms experienced with tamoxifen use were hot flushes (33 *vs* 28.5%) and with exemestane were arthralgia (18.4 *vs* 9.2%). There was more osteoporosis reported for exemestane (4.7 *vs* 2.1%) but no differences in fracture rates.

Dr Dan Rea, Medical Oncologist at Birmingham University Hospital and leader of the UK TEAM study involving 1275 patients, said the study provides important new clinical data. In particular, a British-led substudy of tumour samples analysed for oestrogen and progesterone receptor status showed progesterone receptor status is a prognostic marker of early relapse but does not predict response to treatment.

Olwen Glynn Owen

Zoledronic acid and chemotherapy reduce tumour size more effectively

Adding zoledronic acid (Zometa) to standard chemotherapy before breast cancer surgery reduces the size of breast tumours more effectively than chemotherapy alone in early-stage disease, found a study presented at the San Antonio Breast Cancer Symposium.

Professor Robert Coleman (Sheffield, UK) and colleagues performed a retrospective 'exploratory' pathology analysis on 205 pre- and postmenopausal women receiving neoadjuvant chemotherapy as part of the phase III AZURE study.

In AZURE, 3360 women with stage II or III breast cancer were randomized to standard neoadjuvant chemotherapy, with or without zoledronic acid, given in 19 separate 4 mg doses over 6 months. Each pathology report recorded the size of tumour at excision.

Patients in the zoledronic acid arm of the subgroup analysis had a median residual tumour size of 20.5 mm compared with 30 mm in the chemotherapy alone arm. In a multivariate analysis, taking into account other factors affecting response to chemotherapy, the median minimal residual tumour size was 28.7 mm in patients who received zoledronic acid compared to 42.4 mm in the chemotherapy alone arm (95% confidence interval=5.4–22.9 mm; P=0.002). The number of patients requiring mastectomy was 77.9% in the chemotherapy group *vs* 65.3% in the combination group.

'These data suggest that zoledronic acid is doing something more than just affecting bone,' said Professor Coleman, 'but it is not a practice-changing study; it is a hypothesis generating study.' Future trials will look at this in more detail.

He added that in-vitro data suggest chemotherapy sensitizes tumour cells to the apoptotic effects of zoledronic acid. 'On its own zoledronic acid does not have any appreciable effect. But providing you give zoledronic acid after chemotherapy you achieve an exquisite synergy,' said Coleman.

Janet Fricker

Professor Rob Coleman, Honorary Consultant Medical Oncologist, Weston Park Hospital, Sheffield

SAN ANTONIO BREAST CANCER SYMPOSIUM
SAN ANTONIO, TEXAS, 11–14 DECEMBER

Overall survival indication for aromatase inhibitors

BIG 1-98 data, presented at San Antonio Breast Cancer Symposium, show for the first time a 'suggested' overall survival benefit for the aromatase inhibitor letrozole (Femara) compared to tamoxifen in the adjuvant setting.

The Breast International Group (BIG) 1-98 study of postmenopausal women with hormone receptor-positive early-stage breast cancer was designed to give a head-to-head comparison of letrozole with tamoxifen during the first 5 years following breast cancer surgery, and was later expanded to look at the sequencing of both agents to determine the optimum approach.

In the trial, involving 8014 patients from 27 different countries, women were randomly assigned to one of four treatment regimens: 5 years of tamoxifen only (n=1548), 5 years of letrozole only (n=1546), 2 years of tamoxifen followed by 3 years of letrozole (n=1540) or 2 years of letrozole followed by 3 years of tamoxifen (n=1540). Results were 'complicated' by the fact that about 25% of patients (n=619) in the tamoxifen arm were selectively crossed over to letrozole in 2005 after the study was unblinded.

The intent to treat analysis for monotherapy showed that at a median follow-up of 76 months, patients taking letrozole had a 13% reduction in the risk of death compared to those taking tamoxifen (hazard ratio=0.87, 95% confidence interval=0.75–1.02, P=0.08). Letrozole also showed a long-term benefit in reduced disease-free survival events by 12% (P=0.03, hazard ratio=0.88, 95% confidence interval=0.78–0.99), and reduction of distant metastases by 15% (P=0.05, hazard ratio=0.85, 95% confidence interval=0.72–1.00).

To explore the impact of selective crossover, an additional 'censoring' analysis was conducted, where the study ceased to follow the tamoxifen patients who had been switched. A 19% reduction in the risk of death was observed in favour of letrozole (hazard ratio=0.81, 95% confidence interval=0.69–0.94).

'The true hazard ratio is likely to lie somewhere between these two results,' said Henning Mouridsen, from Copenhagen University Hospital, Denmark, who presented the results.

Also presented were the sequential treatment analysis results of BIG 1-98, which showed the 5-year disease-free survival rates were 87.9% for those receiving letrozole only, 86.2% for those receiving 2 years of tamoxifen followed by 3 years of letrozole and 87.6% for those patients receiving 2 years of letrozole followed by 3 years of tamoxifen.

'We found that it appears to be better to start treatment with letrozole and continue for 5 years, but if necessary patients can switch to tamoxifen after 2 years without loss of efficacy,' said Professor Alan Coates, the BIG 1-98 scientific committee co-chairman from the University of Sydney, Australia.

Janet Fricker

Axillary ultrasound and cytology in assessing nodal status

A team from the University Hospital of South Manchester compared preoperative axillary assessment using ultrasound cytology with eventual histopathological results to identify the accuracy of preoperative axillary node assessment.

Preoperative axillary ultrasound was used to identify suspicious or malignant nodes which were then confirmed with cytological assessment to allow management decisions regarding axillary clearance or sentinel node biopsy.

Overall 79/365 (21%) early breast cancer patients had suspicious or malignant nodes on ultrasound, of which 78 were confirmed on cytology, thus avoiding unnecessary sentinel node biopsy. Ultrasound and cytology accurately identified patients with ER (oestrogen receptor)-negative (P=0.001), high grade (P=0.001) and large size tumours 20 mm (P=0.001), with involved nodes. Only 11% of ER-negative compared to 46% of ER-positive tumours were incorrectly classified (P=0.002). ER-positive, low grade, small tumours were most likely to have a false negative axillary assessment. Specificity of cytological assessment of nodes was 99% and sensitivity 54%.

Axillary ultrasound combined with cytological assessment of suspicious nodes accurately identifies most women who require axillary clearance.

Gene expression test predicts distant recurrence

Researchers from the Royal Marsden Hospital in London have demonstrated that the Oncotype DX recurrence score result is a significant independent predictor of distant recurrence in both node-negative and node-positive, hormone receptor-positive breast cancer patients who are treated with anastrozole or with tamoxifen.

Oncotype DX is a multigene expression test used to predict the likelihood of chemotherapy benefit as well as the likelihood of recurrence for women with early stage breast cancer. In a prospective study, researchers used Oncotype DX to analyse tumour samples from 1231 patients in the ATAC trial.

'Our multivariate analysis confirms that along with other standard measures Oncotype DX contributes independently to providing a more complete picture of prognosis,' said Dr Mitch Dowsett, Royal Marsden Hospital and Team Leader at the Breakthrough Breast Cancer Research Centre in London.

'Physicians can take this information into account when making chemotherapy treatment decisions for both node-negative and node-positive early stage breast cancer patients planned for either anastrozole or tamoxifen treatment,' concluded Dr Dowsett.