Ultra-low dose hormones 'future' of symptom relief in menopause

International menopause specialists say ultra-low dose versions of hormone replacement therapy are now the best way forward for relieving menopausal symptoms while minimizing the risk of side effects, including cardiovascular disease, venous thromboembolism and breast cancer.

Very low dose preparations, with a mere 25% of doses of oestradiol and progestogen used routinely 20 years ago, are now being extensively studied for efficacy and for their impact on side effects associated with higher doses of hormone replacement therapy.

Dose reductions are consistent with regulatory requirements to prescribe symptomatic women the lowest possible doses of hormone replacement therapy for as short a time as possible.

Speaking at the 12th World Congress on the Menopause, in Madrid (19–23 May), Dr David Sturdee, Consultant Gynaecologist at Birmingham Heartlands and Solihull Hospitals and President Elect of the International Menopause Society, said new ultra-low dose combinations of 17beta-oestradiol 0.5 mg with either 0.1 mg or 0.25 mg norethisterone acetate show statistically significant differences from placebo in reducing hot flushes, alleviating sleep problems and achieving amenorrhoea.

The low-dose preparations were compared against placebo in a three-arm, 6-month placebo-controlled randomized double-blind study, CHOICE (Clinical Study on Hormone Dose Optimisation in Climacteric Symptoms). The study involved 577 postmenopausal women between 44 and 65 years of age who were suffering around 70 moderate to severe hot flushes weekly.

'Even at these low doses we saw a gratifying reduction in hot flushes. Active treatment reduced these to 20 or fewer,' noted Dr Sturdee.

No impact of ultra-low dose hormone replacement therapy was seen on lipids, weight or on endometrial hyperplasia and women experienced amenorrhoea to virtually the same extent as those on placebo.

Ultra-low dose hormone replacement therapy formulations are also being viewed as a means of controlling menopausal symptoms without stimulating the breast and possibly increasing the incidence of breast cancers.

Professor Bo von Schoultz of the Karolinska Institute, Stockholm, Sweden studied mammograms of a subpopulation of patients from the CHOICE study that included 255 postmenopausal women in Scandinavia.

Mammograms were conducted before and after ultra-low dose hormone replacement therapy was prescribed.

Professor von Schoultz found that ultra-low dose hormone replacement therapy does not cause the mammographic breast density commonly experienced with higher doses and which is associated with symptoms of mastalgia – pain and soreness. He also found no evidence of cell proliferation. 'Overall its effects on the breast are neutral,' he concluded.

Olwen Glynn Owen

'Innovative agent' for lymphoma

New data from the First-Line Indolent Trial (FIT) show that health-related quality of life parameters were similar between patients receiving consolidation with 90-Y]-ibritumomab tiuxetan and those receiving no further treatment.

The data were presented at the International Congress on Malignant Lymphomas in Lugano, Switzerland. Presenting the results, the investigators said that the data provide some reassurance to clinicians and patients over the use of 90-Y]-ibritumomab tiuxetan as consolidation treatment in advanced-stage follicular lymphoma.

Last month, marketing authorization for 90-Y]-ibritumomab tiuxetan was extended for first-line consolidation use.

Professor of targeted therapy and oncology at the Christie Hospital in Manchester, Professor Tim Illidge, said: 'The availability of 90-Y]-ibritumomab tiuxetan as consolidation therapy provides clinicians with an innovative treatment option that could help follicular lymphoma patients extend life without disease progression.'

The FIT trial, presented at the 49th Annual Meeting of the American Society of Hematology and reported in *BJHM* in February, showed that a single infusion of this radioimmunotherapy agent given to patients with advanced follicular lymphoma who had only partially responded to induction therapy brought three-quarters into complete remission.

Rhonda Siddall

Abdominal X-ray can predict dialysis patients' mortality

An abdominal aortic X-ray is a simple, low-cost prognostic indicator of mortality in dialysis patients, new data have suggested.

Results from the CORD study, presented at the XLV European Renal Association-European Dialysis and Transplant Association meeting in Stockholm, showed that 24% of dialysis patients with aortic calcification at baseline died compared to only 6% of dialysis patients with no aortic calcification at baseline over 2 years. Aortic calcification was assessed by X-ray at baseline and 24 months later.

Dr Eero Honkanen, Helsinki University Central Hospital

Presenting the data Dr Eero Honkanen from Helsinki University Central Hospital said: 'A simple X-ray gives us an insight into progression and may help clinicians to select treatment options accordingly.'

The study of 454 patients showed that aortic calcium calcification progressed significantly more in patients with calcification at baseline than in those without.

Rhonda Siddall

First UK guidelines on kidney cancer treatment

Five UK renal cancer experts are spearheading the production of the first UK guidelines for treating metastatic renal cell carcinoma. At an initial roundtable meeting in London in May, the experts resolved to form a writing group to develop guidelines.

Meeting chair Dr Paul Nathan from Mount Vernon Hospital, Northwood, Middlesex, said: 'With four new targeted treatments for kidney cancer currently available and more on the way we felt it imperative to produce a working document to help inform everyone involved in the decision-making process. That includes clinicians and commissioners. With no guidelines currently available in the UK for renal cell carcinoma we want to disseminate best practice.'

In addition to Dr Nathan, the independent writing group will consist of Professor Tim Eisen from Cambridge Cancer Centre, Professor John Wagstaff from Swansea School of Medicine, Dr Emilio Porfiri from University Hospital, Birmingham, and Dr Tom Powles from Barts and the London NHS Trust.

The expert group plan to develop treatment algorithms based on the highest quality of evidence, with additional information on prognostic grouping and histological subtypes. In a fast-moving field, they feel such guidelines should be updated regularly.

The four new treatments (sunitinib, sorafenib, bevacizumab/interferon alpha and temsirolimus) are currently being considered by the National Institute for Health and Clinical Excellence (NICE) in a technology appraisal for targeted therapies in advanced renal cell cancer, with draft guidance expected in July.

'In the USA and most of Europe these drugs are standard care,' said Dr Nathan. 'We are concerned that if the drugs are turned down by NICE the standard of care for renal cancer patients in the UK will be significantly lower than that of other developed countries.'

Janet Fricker

New obesity treatment improves glucose control

The National Institute for Health and Clinical Excellence (NICE) has issued new guidance recommending use of Acomplia (rimonabant) in England and Wales, within its licensed indications, as an adjunct to diet and exercise for adults who are obese or overweight and who have had an inadequate response to, are intolerant of or are contraindicated to other anti-obesity agents that have previously been reviewed by NICE.

In clinical trials in obese and overweight patients, many of whom had associated risk factors such as type 2 diabetes, Acomplia was shown to help people to not only lose weight but also to improve their cardiovascular risk profile above and beyond that expected from weight loss alone.

Among patients with type 2 diabetes not currently treated with antidiabetic medicines, those given Acomplia experienced significant improvements in weight and blood sugar control as well as other risk factors such as high-density lipoprotein cholesterol and triglycerides compared to those on placebo.

Dr David Haslam, Clinical Director of the National Obesity Forum, welcomed the new NICE guidance, saying: 'Obesity is a chronic disease that places a significant burden on society as well as an individual, so it is vital GPs have a full range of options to help treat obese and overweight patients especially those with associated risk factors such as type 2 diabetes.

'Today's new guidance from NICE is of real benefit to doctors trying to manage this growing group of patients,' he continued.

The results of ARPEGGIO, the first trial of rimonabant in patients with type 2 diabetes, not adequately controlled with insulin therapy, were presented at the 68th American Diabetes Association meeting, in San Francisco in June.

Rimonabant 20 mg significantly improved glycosylated haemoglobin levels by 0.89% from the baseline value, and 0.64% over the control group ($P<0.0001$).

Rimonabant tripled the number of diabetic patients reaching the 7% glycosylated haemoglobin level recommended by international medical guidelines. These data indicate an improvement in glycaemic control with rimonabant 20 mg in type 2 diabetic patients inadequately controlled with insulin.

'The ARPEGGIO trial demonstrated that there is still room for significant improvement in diabetic patients who, despite several years of standard therapies including insulins, in addition to diet and exercise measures, are not well controlled', declared Priscilla L Hollander, Baylor University Medical Center, Dallas, Texas, USA, and Coordinating Investigator of the study.

Increased survival in early-stage pancreatic cancer

Gemcitabine improves overall survival in early-stage pancreatic cancer, according to new data presented at ASCO.

The CONKO-001 trial is the first large-scale phase III trial to show a benefit for any chemotherapy agent in early-stage pancreatic cancer.

Rhonda Siddall

Once-daily treatment for overactive bladder

Pfizer have launched Toviaz (fesoterodine fumarate), a new, once-daily, anti-muscarinic treatment for overactive bladder – a condition affecting 4.9 million people in the UK.

Toviaz is available as a 4 mg and 8 mg dose, allowing flexible dosing.

Reducing kidney damage in type 2 diabetes

Results from a new sub-analysis of the data from ADVANCE, the world's largest-ever study of diabetes, show that the blood pressure-lowering drug Preterax (perindopril/indapamide) reduces the development of kidney damage in patients with type 2 diabetes by nearly one third.

It also leads to the regression of kidney disease in about one in six patients with existing kidney disease.

AMERICAN SOCIETY OF CLINICAL ONCOLOGY
CHICAGO, 30 MAY–3 JUNE

Prolonged progression-free survival in metastatic breast cancer

Continuing treatment with Herceptin (trastuzumab) increases progression-free survival in women with advanced HER2-positive breast cancer requiring additional treatment after their cancer has progressed during previous trastuzumab treatment, show results from the first randomized study to assess this issue.

The GBG-26 study randomized 156 women with HER2 positive locally advanced or metastatic breast cancer who had previously been treated with first-line trastuzumab, with or without chemotherapy, to continue with trastuzumab (6 mg/kg body weight every 3 weeks) plus capecitabine (2500 mg/m^2 on days 1–14, every 21 days) or to capecitabine alone.

Results showed that time to disease progression was nearly 3 months longer in women treated with trastuzumab plus capecitabine compared to chemotherapy alone (8.2 months *vs* 5.6 months; P=0.034). Continuation of trastuzumab nearly doubled the number of patients responding to treatment from 27.0% to 48.0%.

Reporting the findings, Professor Gunter von Minckwitz, from the University Women's Hospital, Frankfurt, Germany, said: 'The GBG-26 study confirms that trastuzumab continues to target and shrink HER2-positive breast cancer even beyond progression, when combined with another chemotherapy.'

Data on adverse events showed a small increase in side effects, with a 2.5% increase in grade III cardiac dysfunction in women treated with trastuzumab plus capecitabine. This was in line with previous data.

Dr David Miles, Consultant Medical Oncologist at Mount Vernon Hospital, London, agreed. 'GBG-26 confirms the benefit of what many people are already doing – continuing with Herceptin in women whose cancer is progressing. HER2 is the primary driver of HER2-positive breast cancer, so we need to keep the HER2 brake on. The study shows that this is the right thing to do.'

Susan Mayor

Sutent gives metastatic renal cancer patients over 2 years survival

Patients with metastatic renal cell cancer treated with first-line sunitinib malate (Sutent), an orally-administered multi-targeting small molecule tyrosine kinase inhibitor, are likely to survive for over 2 years, according to results of a landmark study.

Investigators say a survival outcome exceeding 2 years breaks new ground for metastatic renal cell cancer and that this is double the time expected from the previous standard therapy, interferon alpha.

Overall survival data from a phase III 750-patient double-blind randomized study of first-line sunitinib *vs* interferon alpha in treatment of metastatic renal cell cancer were presented by Dr Robert Figlin of the City of Hope National Medical Center, Duarte, California.

Patients receiving interferon alpha could cross over to sunitinib if their disease progressed, and those receiving sunitinib were also able to access different treatments if required.

Among patients who received only the treatment to which they were randomized, overall survival was 28.1 months with sunitinib *vs* 14.1 months with interferon alpha (P=0.0033). The intention to treat analysis, however, showed median overall survival was 26.4 months for patients initially randomized to sunitinib, compared to 21.8 months in those patients initially randomized to interferon alpha, giving a hazard ratio of 0.82 (P=0.051). Sunitinib was given as a 50 mg oral tablet once daily, for 4 weeks, with a 2-week break between cycles. Interferon alpha 9 MU was administered subcutaneously three times per week.

The study previously reported highly significant results for sunitinib in improving progression-free survival and response rates *vs* interferon alpha. Updated efficacy data show the median progression-free survival was 11 months for sunitinib and 5 months for interferon alpha (P<0.000001). Independent review found objective response rates were 39% and 8% respectively.

The data confirm sunitinib as the reference standard first-line therapy for advanced renal cancer, Dr Figlin concluded.

Olwen Glynn Owen

'Concerted prodding' will work

A willingness at the heart of central government to address disparities in care and to inequitable access to expensive cancer drugs exists, such that new policies are inevitable if clinicians and patients 'keep prodding'.

That was the view of Professor Jonathan Waxman, Professor of Oncology at the Hammersmith Hospital, speaking at a workshop on access to cancer care.

'There is a willingness to respond to the right sort of concerted prodding. The government is looking for solutions,' added Professor Waxman. He said that it was easy to take a swipe at the government when high-profile cases hit the media about denial of life-saving treatment. 'But this government is responsible for an almost doubling in the proportion of gross domestic product spent on health care and there have been 407 sets of NICE guidance on cancer care,' said Professor Waxman.

He cited devolved decision making as a key barrier to equitable access. 'Coupled with a rise in GDP has been a six-fold increase in the cost of administration at the primary care level. Processes at the local level are too bureaucratic and decisions are being taken out of the hands of clinicians. This needs to change,' concluded Professor Waxman.

The workshop was sponsored by Pfizer.

Rhonda Siddall

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Overall survival benefit in advanced non-small-cell lung cancer

Late-breaking data reported for the phase III FLEX (First-line in Lung cancer with ErbituX) trial showed a significant overall survival benefit for non-small cell lung cancer patients when the epidermal growth factor receptor (EGFR) inhibitor cetuximab (Erbitux) was added to platinum-based chemotherapy. Benefit was seen across all histological subtypes and occurred irrespective of age, gender, smoking status and tumour size.

The trial, considered one of the highlights of this year's ASCO, included 1125 previously-untreated patients with advanced (stage IIIB/IV) non-small cell lung cancer and tumours expressing EGFR. Patients with all non-small cell lung cancer histological types were included. Patients randomized to cetuximab/cisplatin/vinorelbine survived 1.2 months longer than patients randomized to chemotherapy alone (11.3 *vs* 10.1 months, hazard ratio 0.87, P=0.04).

One-year survival rates were 47% and 42% respectively, response rates overall were 36% *vs* 29% (P=0.01) and time to treatment failure was 4.2 *vs* 3.7 months (P=0.01). Progression-free survival was the same for each treatment arm. Side effects in cetuximab-treated patients were as expected, said investigators, the most frequent being acne-like rash.

Lead investigator Professor Robert Pirker of Medical University of Vienna, Austria, said: 'The data set a new standard for treating newly-diagnosed patients with advanced non-small cell lung cancer.

'This is the first trial of a front-line targeted therapy to include patients with squamous cell carcinomas, and patients who have a particularly poor prognosis,' he pointed out. Almost all patients (94%) had stage IV metastatic disease and 17% had an ECOG performance status of 2.

Current standard first-line targeted therapy and chemotherapy treatment in non-small cell lung cancer includes the anti-angiogenesis agent bevacizumab (Avastin) and a carboplatin/paclitaxel combination. The US E4599 trial, published 2 years ago, showed a 2-month survival benefit over chemotherapy alone (12.3 *vs* 10.3 months). However, the trial excluded patients with squamous cell cancers and patients with ECOG performance status 2, and increased risk of treatment-related death. The European trial, AVAIL, of bevacizumab plus a gemcitabine/cisplatin combination failed to show an overall survival benefit.

Discussing FLEX in the plenary session Professor Thomas Lynch of Harvard Medical School commented that high costs of improving survival with monoclonal antibody therapies were driving research for biomarkers to identify patients most likely to benefit.

EGFR gene amplification detected by fluorescence in-situ hybridization was a leading candidate for pre-selecting patients for cetuximab, he suggested. The presence of K-RAS wild type genes also predicts a good response to cetuximab.

Olwen Glynn Owen

Avastin enables surgery in 'inoperable' colorectal cancer patients

More than one in ten patients with inoperable colorectal cancer were able to undergo surgery to remove cancer that had metastasized to their liver after treatment with bevacizumab (Avastin) plus chemotherapy reduced tumour size, according to results from the First BEAT study.

Of 1914 patients enrolled in the study 11.2% (215) were able to undergo surgery to remove cancer that had metastasized to their liver. Of these, 170 had no residual cancer after surgery. The overall survival data are not yet mature, but 89% of the patients undergoing complete resection were still alive. No clinically meaningful increases in wound-healing complications or bleeding events were seen with bevacizumab.

Professor Jim Cassidy, from Cancer Research UK, Glasgow reported the findings, saying: 'Our results show that bevacizumab-based therapy in patients with initially unresectable disease does not preclude patients from undergoing subsequent metastasectomy with curative intent.'

A second registry study, BRiTE, showed that continuing bevacizumab beyond disease progression significantly increased overall survival. The registry included 1953 patients with colorectal cancer who were treated with the angiogenesis inhibitor. At first progression, 642 continued with bevacizumab, while 253 had no treatment and 531 had other treatment. The median overall survival was 19.2 months in patients who continued bevacizumab post-progression *vs* 9.5 months in those who stopped the drug (hazard ratio 0.48).

Professor Josep Tabernero, from the Vall d'Hebron University Hospital, Barcelona, said: 'The data clearly suggest that continuing Avastin after progression from its use in a first-line setting is very beneficial.'.

Susan Mayor

Improved survival in advanced liver cancer

Further data that sorafenib improves overall survival in patients with advanced liver cancer were announced at ASCO. The phase III data in 226 Asian patients with advanced liver cancer who had not received prior systemic therapy showed that sorafenib improved overall survival by 47.3% (median 6.5 months *vs* 4.2 months for placebo, P=0.014).

UK liver specialists said the data provide further evidence supporting a survival benefit for sorafenib in advanced liver cancer. The SHARP study, reported at last year's ASCO, showed that sorafenib extended overall survival in patients with liver cancer *vs* those taking placebo by 44% (hazard ratio=0.69; P=0.0006).

Rhonda Siddall