New option for chronic lymphocytic leukaemia

The monoclonal antibody alemtuzumab has been granted a first-line licence following data showing superior progression-free survival in chronic lymphocytic leukaemia patients compared to chlorambucil.

Professor Peter Hillmen, consultant haematologist at the Leeds Teaching Hospitals NHS Trust, said: 'This is a significant advance for patients with this condition as it provides a new option for those who are not suitable for treatment with fludarbine combination chemotherapy.'

Professor Hillmen was the principal investigator of the recently published randomized trial to evaluate the efficacy and safety of intravenous alemtuzumab compared with chlorambucil in first-line treatment of chronic lymphocytic leukaemia (Hillmen et al, 2007). The study found that progression-free survival was reduced by 42% (P=0.0001) with alemtuzumab treatment relative to chlorambucil. The median time to alternative treatment was 23.3 months for alemtuzumab and 14.7 months for cholorambucil (P=0.0001). Adverse event profiles were similar, but with more infusion-related and cytomegalovirus events with alemtuzumab and more nausea and vomiting with cholorambucil.

New guidelines published in *Blood* have raised the spectre of a targeted approach to alemtuzumab use. The guidelines from the International Workshop on Chronic Lymphocytic Leukaemia say that fluorescent in situ hybridization (FISH) testing can be used to detect chronic lymphocytic leukaemia cells that have 17p deletion which is associated with an inferior prognosis and poor response to standard chemotherapy.

Professor Hillmen, one of the experts responsible for drawing up the new guidance, said there is increasing evidence that detection of some chromosomal deletions have prognostic significance and may influence therapeutic decisions. The guidelines recommend FISH testing before treatment for any patient in a clinical trial and for subsequent second- and third-line treatment.

Rhonda Siddall

Hillmen P, Skotnicki AB, Robak T et al (2007) Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol* **25**(35): 5616–23

Surgical ward screening for MRSA is of 'no benefit'

New research has cast some doubt as to whether the use of an early screening strategy to reduce nosocomial MRSA (meticillin-resistant *Staphylococcus aureus*) infections in surgical patients is justified. A prospective, crossover, cohort study compared the effect of two infection control strategies in 21 754 patients admitted to one of 12 surgical wards for more than 24 hours (Harbarth et al, 2008).

Rapid screening failed to reduce the rate of development of nosocomial MRSA infection when compared to standard infection control measures alone (1.11 per 1000 patient days *vs* 0.91 per 1000 patient days, adjusted incidence rate ratio 1.20; 95% confidence interval 0.85–1.69, P=not significant).

This outcome was unaffected after adjustment for colonization pressure, antibiotic selection pressure, use of alcohol-based hand rubs, temporal trends, and potential clustering effects.

The study authors report that 57% of infected patients were MRSA-free on admission, but acquired MRSA infection during hospitalization, demonstrating the 'limited value of screening on admission for patients hospitalised for extended periods in surgical services that do not perform weekly surveillance cultures'.

However, they also highlighted the following:

- MRSA rates at the study centre were relatively low for a surgical department, making detection of a significant treatment effect less likely
- The positive results for 31% of patients were only available after surgery
- 34% of patients with an MRSA surgical site infection did not receive antibiotic prophylaxis covering MRSA (some surgeons being reluctant to add vancomycin to the standard prophylactic regimen.

They commented that although many policy makers call for universal MRSA screening at hospital admission, the effectiveness of this on patient outcomes had not been tested.

To increase effectiveness, they suggest that MRSA screening could be targeted to surgical patients who undergo elective procedures with a high risk of MRSA infection – and that surgical services and infection control teams should carefully assess their local MRSA epidemiology and patient profiles before introducing a universal screening policy.

Stephen Pinn

Harbarth S, Fankhauser C, Schrenzel J et al (2008) Universal screening for MRSA at hospital admission and nosocomial infection in surgical patients. *JAMA* **299**(10): 1149–57

Early follow up after myocardial infarction

Follow up within a month of discharge after an acute myocardial infarction is more likely to lead to effective medication 6 months later, according to a cohort study from a US prospective study of acute myocardial infarction patients (Daugherty et al, 2008).

Analysis of 1516 patients in the Prospective Registry Evaluating Outcomes After Myocardial Infarction: Events and Recovery suggested that 98% were candidates for aspirin, 96% for beta-blockers, 44% for statins, and 41% for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, more than a third of patients (34%) reported no relevant follow up in the first month after discharge.

Those followed up within the first month were more likely to be prescribed beta-blockers, aspirin or statins at 6 months, and there was an indication of lower mortality at 6 months in this group.

The authors conclude that early follow up after discharge post-myocardial infarction is associated with greater use of guideline-recommended therapy, supporting current recommendations that patients should be followed up within several weeks of discharge.

Stephen Pinn

Daugherty SL, Ho PM, Spertus JA et al (2008) Association of early follow-up after acute myocardial infarction with higher rates of medication use. *Arch Intern Med* **168**: 485–91

Women need cholesterol check post-menopause

Health-care professionals are failing to take into consideration the influence that menopause has on cholesterol levels, concludes *Check for Change*, a report commissioned by Flora pro-activ and supported by H.E.A.R.T. UK calling for cholesterol checks to become routine for all women over 45 years of age.

A survey of 150 health professionals and 500 women aged between 45 and 65 years, accompanying the report, found that only 15% of health-care professionals were aware that women of menopausal age are at equal (or greater) risk of cardiovascular disease as middle-aged men. Furthermore, only 7% of women in the target age group reported having been advised to have cholesterol levels checked by their doctor.

Dr Heather Currie, a gynaecologist and obstetrician from Dumfries and Galloway Royal Infirmary, and one of the authors of the report, said: 'As health-care professionals, we have a duty to let menopausal women know that high cholesterol, triggered by the loss of oestrogen, is a significant threat to their health. We need to look beyond the short-term effects of the menopause to the more serious long term metabolic changes. Menopause symptoms should prompt doctors to screen for cardiovascular risks, and to give women advice on controlling modifiable risk factors such as elevated cholesterol and hypertension.'

Gynaecologists and other hospital doctors treating menopausal women, she added, have an important role to play, and should not lose the opportunity of advising patients on cholesterol.

The menopause, says the report, results in a shift in fat distribution from the woman's lower body to the upper body, leading to a central lipid redistribution characteristic of metabolic syndrome. Furthermore an abnormal lipid profile develops in menopausal women, with low-density lipoprotein cholesterol and triglyceride levels increasing and high-density lipoprotein cholesterol decreasing.

Levels of low-density lipoprotein cholesterol in women undergoing menopause increase by between 10 and 20%, with the average cholesterol level for a woman aged between 55 and 64 years being 6.3 mmol/litre. Epidemiological studies have estimated that a 10% decrease in cholesterol reduces the risk of coronary heart disease by 20%.

'Following the HRT [hormone replacement therapy] debacle menopause has become a neglected area,' says Dr Currie. 'But health professionals need reminding that the increased risk of heart disease is still there, and that heart protection should be put back on the agenda.'

Janet Fricker

Novel bioabsorbable stents are a pace apart

Promising outcomes have been reported following the feasibility study of a novel bioabsorbable drug-eluting stent for patients with single de-novo coronary artery lesions.

In ABSORB, 30 patients with either stable, unstable or silent ischaemia and a single de-novo lesion that was suitable for treatment with a single 3.0x12 mm or 3.0x18 mm stent were recruited from four academic centres in New Zealand, the Netherlands, Poland and Denmark.

Procedural and device success rates were high (100% and 94%, respectively). At year 1, the rate of major adverse cardiac events was 3.3%, with only one patient having a non-Q-wave myocardial infarction and no target lesion revascularization. No late stent thromboses were recorded.

The angiographic in-stent late loss was 0.44 mm at 6 months' follow-up, which investigators said was mainly the result of a mild reduction of the stent area as measured by intravascular ultrasound.

The bioabsorbable everolimus-eluting stent has a backbone of poly-L-lactic acid that provides the support, and a coating of poly-D L-lactic acid that contains and controls the release of the antiproliferative agent, everolimus.

The authors commented that these early data confirm acceptable in-stent late loss, minimal intra-stent neointimal hyperplasia, and a low stent area obstruction with the novel device.

Stephen Pinn

Ormiston JA, Serruys PW, Regar E et al (2008) A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet* **371**: 899–907

Long-acting injections reduce hospital admissions

Data published in the *Journal of Psychopharmacology* show that the number of hospital admissions for people diagnosed with schizophrenia is significantly reduced after starting treatment with risperidone long-acting injections.

Falls prevention strategy failing elderly in hospital

Short-stay elderly patients do not benefit from a targeted falls prevention programme, according to research in the *British Medical Journal*. Nearly 4000 elderly patients with a median hospital stay of 7 days were studied. No difference was documented in fall rates between intervention and control wards during follow up.

Reducing the risk of breast cancer recurrence

Research published in the *Journal of Clinical Oncology* shows treatment with the aromatase inhibitor Femara (letrozole) after 5 years of tamoxifen therapy, anywhere from 1 to 7 years later, reduces the risk of breast cancer returning by 63% and of the cancer spreading to other areas of the body by 61% at a median follow up of 2.8 years.

Early breast cancer: are START radiotherapy data too good to be true?

Doubts have been cast about the validity of new data showing that radiotherapy for breast cancer patients can be delivered as a lower overall dose in fewer, larger doses, giving similar tumour control and fewer adverse side effects than current best practice (www.thelancet.com published online March 19 2008).

The international standard radiotherapy schedule for early breast cancer delivers 50 Gy of radiation in 25 fractions of 2·0 Gy over 5 weeks. However, cancer specialists in the UK have long believed that a lower total dose delivered in fewer, larger fractions can be at least as safe and effective as the standard.

START (Standardisation of Breast Radiotherapy Trial) was jointly funded by Cancer Research UK, the UK Medical Research Council, and the UK Department of Health, and involved researchers from 35 UK cancer centres.

In Start A, 2236 women were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2·0 Gy (749 women) *vs* 41·6 Gy in 13 fractions of 3·2 Gy (750 women) or 39 Gy in 13 fractions of 3·0 Gy (737 women).

Professor John Yarnold from the Institute of Cancer Research and Royal Marsden Hospital and his fellow UK researchers found that the rate of tumour relapse at 5 years was 3·6% after 50 Gy, 3·5% after 41·6 Gy, and 5·2% after 39 Gy. Neither late adverse effects nor local tumour relapse after 41·6 Gy were different compared to 50 Gy.

They concluded: 'A lower total dose (41·6 Gy) in a smaller number of fractions could offer similar rates of tumour control and normal tissue damage as the international standard fractionation schedule of 50 Gy in 25 fractions.'

In Start B, 2215 were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2·0 Gy over 5 weeks (1105 women) and 40 Gy in 15 fractions of 2·6 Gy over 3 weeks (1110 women). The rate of tumour relapse at 5 years was 2·2% in the 40 Gy group and 3·3% in the 50 Gy group.

In the respective START studies, photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy and 40 Gy than with 50 Gy.

The authors concluded: 'After surgery for early breast cancer, a radiotherapy schedule delivering 40 Gy in 15 fractions over 3 weeks seems to offer local regional tumour control and rates of late normal tissue effects at least as good as the accepted international standard of 50 Gy in 25 fractions over 5 weeks."

However, in an accompanying editorial, Dr Harry Bartelink of the Netherlands Cancer Institute, Amsterdam, The Netherlands, and Dr Rodrigo Arriagada of the Institut Gustave Roussy, Villejuif, France, urged caution. 'We realise,' they said, 'that hypofractionation is convenient for patients, because it reduces the number of visits to radiotherapy departments and waiting lists in several cancer centres. Nevertheless we have to wait for data on longer follow up before final conclusions can be drawn from START.'

They pointed out that several studies have shown that reducing the radiation dose per fraction while increasing the number of fractions and the total dose limits normal tissue damage – and, indeed, that in head and neck tumours, this hypofractionation had led to better tumour control and survival without an increase in toxicity.

'We wonder why the outcomes of the START trials show the opposite effect?' they ask. 'Will long-term follow-up show results consistent with those for head and neck cancer, or are the results of the START trials due to different biological features in breast cancer?'

They conclude that: 'We should accept that this result could be a false negative that might change with longer follow up and more events.'

Stephen Pinn

Improving overall survival in colorectal cancer

Irinotecan plus bevacizumab combined with an infusional schedule of fluorouracil (5FU) produces significant improvements in overall survival in patients with metastatic colorectal cancer compared with irinotecan plus bevacizumab plus bolus 5FU, reports the latest finding of the BICC-C study, published in the *Journal of Clinical Oncology*.

The investigators initially set out to compare the safety and efficacy of different irinotecan regimens in first-line treatment of metastatic colorectal cancer, with irinotecan plus infusional 5FU and leucovorin (FOLFIRI), and irinotecan plus bolus 5FU and leucovorin (IFL).

However, following the Food and Drug Administration's approval of bevacizumab, the investigators, led by Charles S Fuchs from Dana-Farber Cancer Institute, Boston, USA, amended the trial to include bevacizumab. A total of 57 patients were randomly assigned to the FOLFIRI+bevacizumab arm (using a continuous infusion of 5FU), and 60 patients were assigned to irinotecan plus bolus 5FU/leucovorin.

Patients receiving FOLFIRI +bevacizumab had a median overall survival of 28.0 months compared to 19.2 months for patients who received bolus IFL (P=0.037). The proportion of patients alive at 1 year was 87% for the FOLFIRI+bevacizumab group compared to 61% for the IFL group (P=0.01). The mortality at 60 days was 1.8% for patients who received FOLFIRI+bevacizumab compared to 6.8% for patients who received bolus IFL.

'Consequently, when using an irinotecan-based regimen in the treatment of first-line metastatic colorectal cancer, an infusional schedule of FU should be the preferred approach,' write the authors.

Commenting on the study Dr Markus Moehler, from Johannes-Gutenberg University, Mainz, Germany, said: 'Bolus 5FU is known to be more toxic than continuous 5FU, with bolus regimens more likely to cause gastrointestinal side effects and cardiovascular toxicities. The survival data are very encouraging. FOLFIRI plus bevacizumab should become one of the new standards of care for patients with unresectable metastatic colorectal cancer.'

Janet Fricker

Fuchs CS, Marshall J, Barrueco J (2008) Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. *J Clin Oncol* **26**(4): 689–90

1ST OVARIAN CANCER ACTION INTERNATIONAL CONFERENCE
LONDON, 7–8 MARCH

Gene mutation gives better outcomes for ovarian cancer patients

Ovarian cancer patients with the 'BRCAness' syndrome, who carry mutations of the Breast Cancer associated genes 1 and 2, are likely to have a better treatment outcome than patients without these mutations, according to a study from The Royal Marsden Hospital, London. (These genes are different from the Ashkenazi Jewish BRCA genes which also confer a survival advantage.)

Professor Martin Gore said a retrospective case control study of 66 patients of median age 50 with advanced serous epithelial ovarian cancer (22 with, and 44 without, hereditary mutations of the BRCA genes 1 and 2) was conducted to examine differences in the course of their disease 'journey'. Patients were matched for stage, histological subtype, age at diagnosis and year of diagnosis, and were followed for up to 10 years (average 3.5 years).

Those with the BRCA gene mutations experienced much higher response rates at first and subsequent lines of chemotherapy and longer intervals before relapse, than patients without. 'The remarkable thing was the very high and extremely significant complete response rate – 82% *vs* 43% – these patients achieved with first-line platinum therapy,' he commented. Although patients with BRCA gene mutations did better on all therapies than those without, they had a markedly superior response to further platinum-based therapy (92% *vs* 41% at second-line and 100% *vs* 14% at third-line). Median treatment-free intervals between first and subsequent-line platinum therapies were significantly longer for the BRCA gene mutation patients and they had a significantly longer median survival of almost 6 years (8.4 *vs* 2.9 years).

The implications of these data are that response is a molecular-specific rather than a tumour-specific mechanism, he suggested. Although patient numbers were small they confirm findings of other ovarian cancer studies showing longer progression-free and overall survival in BRCA gene mutation carriers.

The findings underscore the importance of testing for BRCA gene mutations and of treating BRCA mutation-positive patients with platinum therapies. 'Platinum really must be used until refraction and in my view platinum-based therapy must be an arm of any randomized controlled trial involving BRCA mutation patients and novel targeted therapies,' he emphasized.

Olwen Glynn Owen

Ovarian cancer not a silent killer: early detection is vital

The perception that ovarian cancer cannot be detected until it reaches an advanced stage is wrong and misleading to both the public and medical profession, according to the UK cancer tsar Professor Mike Richards. 'Medical students used to be taught that ovarian cancer is a silent killer. In fact it's quite the opposite with multiple early symptoms,' he said. Early detection is key to effective treatment and long survival so awareness of symptoms has to be raised among GPs and the public, he stressed. A retrospective analysis of GPs' patients with ovarian cancer is to examine whether early symptoms such as bloating, abdominal or pelvic pain, polyuria, eating difficulty, and abnormal vaginal bleeding were reported but missed.

Last year in the UK there were 6500 women diagnosed with ovarian cancer and 4460 deaths, he noted. Most presented with stage III disease. One in six is aged under 50 years at diagnosis but almost half are over 70 years of age. Five-year survival in the UK is only 30% compared to 36% in the rest of Europe and 40% in Scandinavia, he remarked. 'The fact that 1-year survival is 70% in Sweden suggests cancer is detected there at an earlier stage than in the UK where 1-year survival is only 60%.'

Efforts to improve screening in the UK will be helped by findings of the UKCTOCS prevalence screen, he said. This randomized 202 638 postmenopausal women to multimodal screening using serum CA125 interpreted with the ROC (risk of ovarian cancer) algorithm, ultrasound or no screening. Women were referred for further tests as necessary and those identified with ovarian cancer underwent treatment. Data presented by Dr Usha Menon of the Institute for Women's Health, UCL, showed multimodal screening had superior specificity and positive predictive value compared to ultrasound. The study will also reveal the impact of screening on survival with results available in 2011.

Olwen Glynn Owen

ERCC1 test predicts platinum resistance

Researchers are developing a means of predicting which ovarian cancer patients are likely to respond poorly to platinum-based chemotherapy. Dr Caroline Michie and colleagues looked at formalin-fixed, paraffin-embedded tumour samples of 145 platinum-treated patients to identify high and low levels of the excision repair cross-complementation group 1 (ERCC1) enzyme associated with platinum resistance in several cancer types.

They compared survival outcomes for patients expressing high or low levels. High ERCC1 expression was associated with worse progression-free and overall survival in patients treated with standard platinum-based chemotherapy. Worse progression-free survival was also seen for carboplatin and paclitaxel. The researchers suggest alternative treatments should be sought for patients with high ERCC1-expressing tumours and tested in a randomized trial against standard therapy.

Olwen Glynn Owen