# newsround

## Selected reports edited by Janet Fricker

### Clinical trials lead to cost savings

British Journal of Cancer

On average, non-commercial oncology clinical trials are associated with small excess treatment costs compared to the standard of care, while commercial trials are associated with high cost savings, concludes a UK study conducted in a single centre. Recruitment of patients to clinical trials was found to be associated overall with considerable cost savings.

It has long been thought that conducting clinical trials incurs additional costs above the standard of care. Such perceptions remain a barrier to academic clinical trials being performed in many countries. In the current study, Pippa Corrie and colleagues, from the Cambridge University Hospitals NHS Foundation, explored the financial implications of conducting clinical trials.

Between January 2009 and December 2010 the team undertook a retrospective cost attribution analysis to determine the treatment costs associated with oncology (non-haematology) clinical trials. At the centre, over the two-year period, 357 cancer patients were recruited to 53 different interventional clinical trials, of which 40 were phase II, two randomised II/III and 11 phase II. Altogether 27 of the trials were academic, non-commercial sponsored trials, and 26 were commercial sponsored trials.

For each protocol, the treatment cost difference for the experimental arm(s) was calculated as the difference between the experimental arm treatment costs and standard of care costs. The costs for cancer drugs were obtained from the British National Formulary (2010).

Results show that, in comparison with the standard of care, the average treatment costs were an excess of £431 (€520) for a non-commercial trial (range £6393 excess to £6005 savings) and a saving of £9294 (€11,215) for a commercial trial (range £0 to £71,489). There was an overall treatment cost saving of £388,719 (€469,000) in 2009 and £496,556 (€599,100) in 2010, largely attributable to provision of free drug supplies from pharmaceutical companies. Overall, the treatment cost savings to the NHS were estimated to be approaching £0.5 million (€0.6 million) per annum.

Notably, seven of the non-commercial trials were associated with treatment cost savings. Two of these trials, SCOT (adjuvant chemotherapy in colorectal cancer) and PERSEPHONE (adjuvant chemotherapy in breast cancer), evaluated whether shorter durations of adjuvant treatment (which cost less) were as effective as the standard of care. Such studies, stress the authors, demonstrate the importance of academic trials, addressing questions that would not represent a priority for industry sponsors.

"In our view, this data provides overwhelming evidence to refute any concern that clinical research generates a cost pressure for the health service. On the contrary, we have demonstrated significant financial gains," write the authors. A balanced portfolio of both commercial and non-commercial research, they add, should offer the greatest benefits to patients and the overall health economy.

E Liniker, M Harrison, JMJ Weaver et al. Treatment costs associated with interventional cancer clinical trials conducted at a single UK institution over 2 years (2009–2010). *BJC* 15 October 2013, 109:2051–57

### Strain analysis reveals subclinical LV dysfunction following anthracyline treatment

European Journal of Cancer

Myocardial strain imaging proved more sensitive than left ventricular ejection fraction (LVEF) in the early detection of left ventricular systolic dysfunction following

anthracycline chemotherapy in HER2/neu-negative breast cancer patients, reports an Australian study.

While anthracycline chemotherapy has remained the cornerstone of breast cancer treatment for four decades, efficacy has been undermined by its dose-dependent cardiotoxicity. In the current study, Paul Stoodley and colleagues, from Liverpool Hospital, Liverpool, Australia, set out to establish whether strain imaging would reveal LV systolic dysfunction not discernible with LVEF in patients with HER2/neu-negative breast cancer up to 12 months after treatment with anthracyclines.

Between October 2008 and March 2011, 78 consecutive anthracycline-naive breast cancer patients were studied prior to the commencement of anthracycline chemotherapy (T1) and within seven days of completing anthracycline therapy (T2). Then in the second part of the study patients found to be HER2/neu-negative were studied at six months (T3) and 12 months (T4) after the initial exam. At these time points LVEF was measured by Simpson's method according to recommendations of the European Association of Echocardiography, while LV longitudinal peak systolic strain (LPSS) was measured with 2D speckle tracking echocardiography.

Altogether 28 of the original 78 participants (36%) were found to be HER2/neu-positive by in situ hybridisation, and therefore proceeded to trastuzumab therapy and were excluded from the analysis at T3 and T4. This left 50 HER2/neu-negative participants who were studied at four time points over 12 months.

Results show that global systolic strain was significantly reduced from a baseline of -19.0±2.3% to -17.5 ± 2.3% immediately after treatment ($P$<0.001), rising by six months to -18.2±2.2% ($P$=0.01). LVEF, on the other hand, remained largely unchanged at both T2 and T3.

By 12 months (T4), global strain had normalised in 84% of patients, with persistent strain remaining in 16% ($n$=8). A re-analysis of data from patients with persistent global strain showed that they had greater reductions in strain at six months (-17.2%), and had received higher cumulative doses of anthracyclines.

"While HER2/neu positive patients treated with adjuvant trastuzumab are monitored closely, we have demonstrated subclinical LV dysfunction by strain analysis in HER2/neu negative patients, who comprise ~75% of all breast cancer patients," write the authors.

Monitoring HER2/neu-negative patients who receive anthracycline therapy at baseline and six months, they add, would help identify patients with subclinical cardiac dysfunction who would benefit from additional cardiac monitoring and treatment.

■ P Stoodley, D Richards, A Boyd et al. Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: A comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months. *Eur J Cancer* November 2013, 49:3396–3403

## Model predicts life expectancy in patients with metastatic cancer

■ Cancer

The TEACHH model is able to divide patients receiving palliative radiotherapy into three distinct life expectancy groups. The approach, suggest the US authors, offers the promise to better tailor palliative therapies to the patient's outlook.

Estimating prognosis is one of the most difficult tasks encountered by oncologists, particularly for patients with metastases whose life expectancy can vary between days and years. But predicting life expectancy has important clinical implications. In an earlier study, Edward Chow and colleagues, from the University of Toronto, created and validated a prognostic model that categorised palliative cancer patients into one of three prognostic groups, using the cancer type (breast vs non-breast), Karnofsky performance status (<70 vs >70) and metastasis location (bone only vs other) (*JCO* 2008, 26:5863–69).

In the current study Monica Krishnan and colleagues, from Dana-Farber Cancer Institute, Boston, Massachusetts, set out to build on the model created by Chow to identify patients at the extreme ends of the prognostic spectrum, i.e. those with short (<3 months) and long (>1 year) life spans.

Between June 2008 and July 2011, the records of 862 patients with metastatic cancer receiving palliative radiotherapy at the Dana-Farber Brigham and Women's Cancer Center were retrospectively reviewed.

Results of a multivariate analysis showed that factors significantly associated with shorter life expectancy were cancer type (lung and other vs breast and prostate), older age (>60 years vs <60 years) liver metastases, Eastern Cooperative Oncology Group performance status (2–4 vs 0–1), hospitalisations within three months before palliative radiotherapy (0 vs >1) and prior palliative chemotherapy courses (>2 vs 0–1).

A further analysis showed that patients in group A who had 0–1 risk factors had a median overall survival of 19.9 months (95%CI, 13.9–31.1 months), that patients in group B who had 2–4 risk factors had a median overall survival of 5.0 months (95%CI 4.3–5.6 months), and that patients in group C who had 5–6 risk factors had a median overall survival of 1.7 months (95%CI 1.2–2.1 months).

"By providing LE estimates, this model may help clinicians provide quality palliative care to their patients with advanced cancer and their families," write the authors, adding that the number of prior palliative chemotherapy courses and hospitalisations have not been reported previously as factors predictive of life expectancy.

The TEACHH model can help identify those patients who are eligible for hospice care and guide end-of-life discussions with patients, it can be used to select hypofractionated RT regimens to avoid protracted courses of RT near death, and to identify those patients with longer life expectancies who may be candidates for dose escalation, which has been associated with improved local control for certain palliative disease sites.

The model, they add, requires external validation to assess its accuracy in disparate settings of patients with advanced cancer presenting for palliative radiotherapy.

■ M Krishnan, Z Epstein-Peterson, Y Chen et al. Predicting life expectancy in patients with metastatic cancer receiving palliative radiotherapy: the TEACHH model. *Cancer*. doi:10.1002/cncr.28408

## Adjuvant gemcitabine improves overall survival in pancreatic cancer

■ JAMA

For patients with macroscopic complete removal of pancreatic cancer, treatment with adjuvant gemcitabine for six months resulted in a 24% improvement in overall survival in comparison to observation alone, report the latest findings of the CONKO-001 study.

The vast majority of pancreatic cancer patients presenting with localised disease allowing surgical resection relapse within two years, leading to five-year survival rates of less than 25%. Although controlled trials have been conducted in the area of adjuvant therapy for almost three decades in such patients, no consensus has been reached on standard approaches to treatment.

In the current CONKO-001 study, Helmut Oettle and colleagues, from the Charité-Universitätsmedizin, Berlin, set out to compare adjuvant intravenous gemcitabine with observation alone in patients undergoing complete, curative-intent resection of pancreatic cancer. The primary endpoint of the study, disease-free survival, has already been reported.

Between July 1998 and December 2004, 368 patients from 88 centres in Germany and Austria were randomised to adjuvant gemcitabine treatment (1g/m$^2$ days 1, 8, 15, q 4 weeks) for six months ($n$=186) or observation ($n$=182). Altogether 179 patients from the gemcitabine arm and 175 patients from the observation arm were eligible for the intention-to-treat analyses of disease-free survival and overall survival. At randomisation, patients were stratified according to tumour stage (T1–2 vs T3–4), nodal status (N0 vs N1), and resection status (R0 vs R1), based on the TNM classification.

By September 2012 (when 89.3% of patients had died), the median overall survival was 22.8 months for the gemcitabine group versus 20.2 months for the observation group (HR=0.76, 95%CI 0.61–0.95, $P$=0.01). As reported previously, median disease-free survival was 13.4 months in the gemcitabine treatment group compared with 6.7 months in the observation group (HR=0.55, 95%CI 0.44–0.69, $P$<0.001). At five years, disease-free survival was 16.6% in the gemcitabine group versus 7.0% in the observation group, while at 10 years, disease-free survival was 14.3% in the gemcitabine group versus 5.8% in the observation group.

The treatment effect was detected consistently across all the pre-stratification subgroups of tumour stage, nodal status, and resection status.

"The statistically significant differences in disease-free and overall survival between treatment groups support the use of gemcitabine as the backbone for future studies of adjuvant therapy following R0/R1 resection of pancreatic cancer," write the authors. Since the study was designed to be applicable to community-based oncologists (without uniform standards for surgery or centralised pathology review), as well as academic centres, they add, the results are likely to be representative of general clinical practice beyond the study countries.

■ H Oettle, P Neuhas, A Hochhaus et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer. The CONKO-001 randomized trial. *JAMA* 9 October 2013, 310:1473–81

## START: 10-year data support hypofractionated radiotherapy for early breast cancer

■ Lancet Oncology

Ten-year follow-up results for the START trials continue to support use of hypofractionated schedules of radiotherapy contracting treatment from five to three weeks following primary surgery in early breast cancer.

In the START studies, following primary surgery, chemotherapy and endocrine treatment, women with completely excised invasive breast cancer from 35 UK radiotherapy centres were randomly assigned, between 1999 and 2002 to different radiotherapy treatment regimens.

The five-year results of the UK Standardisation of Breast Radiotherapy (START) trials suggested that lower total doses of radiotherapy delivered in fewer, larger doses (fractions) were at least as safe and effective as the historical standard regimen (50 Gy in 25 fractions). While the results informed the National Institute for Health and Care Excellence (NICE) and American Society for Radiation Oncology (ASTRO) guidelines for breast radiotherapy fractionation, a 2010 Cochrane review concluded that longer follow-up was needed for a more complete assessment. In the current publication, John Yarnold and colleagues, from the Royal Marsden NHS Foundation, London, report on 10-year data.

In START-A, 2236 women were randomised to receive 50 Gy in 25 fractions (the historical standard), 41.6 Gy in 13 fractions, or 39 Gy in 13 fractions – all delivered over five weeks. The 10-year rates of local-regional relapse were 6.3% for the 50 Gy arm versus 7.4% for the 41.6 Gy arm (HR 0.91, *P*=0.65) and 8.8% for the 39 Gy arm (HR=1.18, *P*=0.41). In comparison to the 50 Gy group, women in the 39 Gy group had significantly less moderate or marked breast induration (*P*=0.034), telangiectasia (*P*=0.003), and oedema (0.001). No significant differences were found between the 41.6 Gy and 50 Gy groups.

In START-B, 2215 women were allocated to receive 50 Gy in 25 fractions over five weeks or 40 Gy in 15 fractions over three weeks. The 10-year local-regional relapse rates were 5.5% for the 50 Gy group versus 4.3% for the 40 Gy group (HR=0.77, *P*=0.21). In comparison to the 50 Gy group, women in the 40 Gy group had significantly less breast shrinkage (*P*=0.015), telangiectasia (*P*=0.032), and breast oedema (*P*=0.001).

"The hypofractionated and control schedules at 10 years remain similar to those at 5 years, confirming that appropriately dosed hypofractionated radiotherapy for women with early breast cancer is safe and effective," write the authors.

In an accompanying commentary, Bruce Haffty and Thomas Buchholz, from Rutgers-Cancer Institute, New Jersey, write that widespread use of a three-week course of radiation might provide patients with more convenient treatment schedules, while reducing health-care costs without compromising patient outcomes.

■ J Haviland, J Owen, J Dewar et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* October 2013, 14:1086–94

## Sentinel lymph nodes: high false-negative after neoadjuvant chemotherapy

■ JAMA

Among women with clinically node-positive (cN1) breast cancer receiving neoadjuvant chemotherapy, who had two or more sentinel lymph nodes (SLNs) examined, the false-negative rate did not meet the predefined study criteria, the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial has concluded. In the phase II trial, use of dual-agent mapping and sampling of at least three SLNs was associated with a lower likelihood of false-negative SLN findings.

While for patients who initially present with node-negative breast cancer, axillary lymph node dissection (ALND) has been replaced by SLN biopsy, the application of SLN for staging the axilla following chemotherapy for women who initially had node-positive cN1 breast cancer remains unclear due to high false-negative rates reported in previous studies.

In the ACOSOG Z1071 trial, Judy Boughey from the Mayo Clinic, Rochester, Minnesota, and colleagues, explored the false-negative rates of SLN biopsy after neoadjuvant chemotherapy, in women who initially presented with cN1 disease. Between July 2009 and June 2011, the investigators enrolled women from 136 institutions who had clinical T0 through T4, N1 through N2, M0 breast cancer and received neoadjuvant chemotherapy. The study protocol was that all SLNs were excised and submitted prior to the ALND procedure. To maximise the likelihood of SLN identification. SLN mapping with both blue dye and radiolabelled colloid mapping agents was recommended.

Results showed that, of the 756 women enrolled, 649 underwent chemotherapy followed by both SLN surgery and ALND. The researchers found that the false-negative rate was 12.6%, which exceeded the prespecified threshold of 10%.

The researchers found that the false-negative rate was 10.8% when a dual-agent mapping technique was used, versus 20.3% when a single agent mapping technique was used (*P*=0.05). Furthermore, the investigators found that the false-negative rate was 9.1% when three or more SLNs were evaluated versus 21.1% when two SLNs were evaluated (*P*=0.007).

"Given this acceptability threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND in this patient population," conclude the authors, adding that after chemotherapy the axilla has more fibrosis, making evaluation of lymphatic drainage and surgical dissection more challenging. Using two mapping agents with different molecular sizes and transit times, they suggest, might offer an important surgical standard for SLN surgery after chemotherapy.

In an accompanying commentary, Monica Morrow and Chau Dang, from Memorial Sloan-Kettering Cancer Center, New York, write that as clinicians move away from the 'one size fits all' approach, prognostic information obtained from residual nodal disease following neoadjuvant therapy is likely to become increasingly important in helping to determine the need for additional therapy. "If that is true, research in ways to improve the performance of SLN biopsy after neoadjuvant therapy is needed for this approach to become a viable management strategy," they write.

■ J Boughey, V Suman, E Mittendorf et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer. The ACOSOG Z1071 (Alliance) Clinical Trial. *JAMA* 9 October 2013, 310:1455–61

■ M Morrow, C Dang. Sentinel node biopsy after neoadjuvant chemotherapy a new standard for patients with axillary metastases? *ibid* pp 1449