NEWSROUND

Selected reports edited by Janet Fricker

Gene alterations influence response to breast cancer chemotherapy

➜ JNCI

Certain gene alterations have been found to improve breast cancer patients' response to anthracycline therapy. The results of a Canadian study show that topoisomerase II alpha (TOP2A) gene alterations (both amplifications and deletions) are associated with an increase in responsiveness to an anthracycline-containing chemotherapy regimen (cyclophosphamide, epirubicin and 5-fluorouracil [CEF]) relative to a non-anthracycline regimen (cyclophosphamide, methotrexate and 5-fluorouracil [CMF]). The results, conclude the investigators, are similar to those seen in patients with HER2 amplification, and suggest that patients with normal breast cancers (without TOP2A or HER2 alterations) should not receive anthracyclines as part of adjuvant treatment.

In the Canadian Mammary 5 (MA.5) trial, women with amplification or overexpression of HER2 were reported to benefit more from adjuvant therapies that included anthracyclines than from non-anthracycline regimens. Since HER2 is located near the gene for TOP2A, it has been suggested that responsiveness to anthracyclines is also associated with TOP2A gene alterations.

To determine such associations relative to TOP2A alterations, Kathleen Pritchard and colleagues, from the University of Toronto (Ontario, Canada), undertook an analysis of data from the MA.5 trial, which had compared CEF with CMF. Tumour samples were available from 438 of the 710 participants in the MA.5 trial, and these were evaluated for TOP2A and HER2 amplification by fluorescence *in situ* hybridisation (FISH).

The results showed that patients with TOP2A gene alterations had 65% better relapse-free survival (adjusted hazard ratio [HR] 0.35, 95% CI 0.17–0.73, P=0.005) and 67% better overall survival (adjusted HR 0.33, 95% CI 0.15–0.75, P=0.008), when treated with the CEF anthracycline-containing regimen than with CMF non-anthracycline-containing regimen.

Conversely, among patients with TOP2A normal tumours, who composed 78% of the breast cancer patients in the study, anthracyclines conferred little or no improvement (HR 0.90 for relapse-free survival and 1.09 for overall survival).

The authors conclude that patients with both TOP2A alteration and HER2 amplification may derive a greater benefit from CEF than from CMF, while those whose tumours lack these features appeared to receive "virtually no benefit" from CEF and could potentially be treated with the less toxic CMF regimen.

The obvious question, say the authors, is which alterations – TOP2A or HER2 – are most closely associated with treatment benefit from CEF. "The small numbers of patients with alterations in both genes made the interpretation of these analyses difficult," they write, adding that larger sample sizes would be needed to provide a definitive answer.

In an accompanying editorial, Dennis Slamon and Michael Press from the University of California, Los Angeles, write: "A question remains as to whether patients with HER2 amplification and TOP2A co-amplification will still benefit incrementally from anthracyclines now that we can use drugs like trastuzumab or lapatinib which target the HER2 alteration directly. This will require analysis of recently completed and ongoing large adjuvant studies that compare anthracycline-based regimens with non-anthracycline regimens in combination with these HER2 antagonists."

■ Topoisomerase II alpha and responsiveness of breast cancer to adjuvant chemotherapy. FP O'Malley, S Chia, D Tu et al. *J Natl Cancer Inst* 6 May 2009, 101:644–650

■ Alterations in the TOP2A and HER2 genes: association with adjuvant anthracycline sensitivity in human breast cancers [editorial]. DJ Slamon and MF Press. *ibid* pp 615–618

Cetuximab benefits colorectal cancer patients without *KRAS* mutations

➜ New England Journal of Medicine

Adding cetuximab to a chemotherapy regimen of FOLFIRI (irinotecan, fluorouracil, plus leucovorin) reduces the risk of progression of metastatic colorectal cancer compared with FOLFIRI alone, according to the findings of the CRYSTAL trial. A subgroup analysis, however, found that benefits from cetuximab were limited to patients with *KRAS* wild-type tumours, and that patients with *KRAS* mutations showed no benefit.

In the CRYSTAL study, Eric Van Cutsem from the University hospital Gasthuisberg (Leuven, Belgium) and collaborators from 201 different international centres, sought to determine whether adding the epidermal growth factor receptor (EGFR) inhibitor to chemotherapy in first-line therapy produced survival benefits. The team also examined the potential of using *KRAS* as a biomarker to predict response to therapy.

In the multicentre phase III study, investigators randomised 1,198 colorectal cancer patients with unresectable metastases to receive cetuximab plus FOLFIRI (*n*=599) or FOLFIRI alone (*n*=599) in 14-day cycles. The study endpoint was progression-free survival time or death within 60 days of randomisation, with progression assessed by CT or MRI. The investigators also conducted a retrospective subgroup analysis to investigate the influence of tumour *KRAS* mutation status on outcome.

Results show that disease progression was observed in 298 patients receiving cetuximab-FOLFIRI and 322 patients receiving FOLFIRI alone, showing a 15% reduction of progression risk for the cetuximab-FOLFIRI group (HR 0.85, 95% CI 0.72–0.99, *P*=0.048). There was no significant difference in overall survival between the two treatment groups: it was 19.9 months for cetuximab-FOLFIRI and 18.6 months for FOLFIRI alone (HR 0.93, 95% CI 0.81–1.07; *P*=0.31).

In the subgroup analysis, where 540 patients were evaluated at baseline to determine *KRAS* mutation status, 348 patients (64.4%) had wild-type *KRAS* and 192 (35.6%) had mutated *KRAS*.

Hazard ratios for progression-free survival among patients receiving cetuximab plus FOLFIRI, as compared with FOLFIRI alone, were 0.68 (*P*=0.02) for people who had tumours with wild-type *KRAS*, and 1.07 (*P*=0.75) for people with mutant *KRAS* tumours.

In the study overall, grade 3 or 4 adverse events occurred in 79.3% of the cetuximab-FOLFIRI group and 61% of the FOLFIRI alone group.

"This trial provides confirmation that, as compared with FOLFIRI alone, cetuximab plus FOLFIRI reduces the risk of progression of metastatic colorectal cancer when used as the first-line treatment and that this benefit is seen mainly in patients with wild-type *KRAS* tumors," conclude the authors.

The observation that there were no significant differences in overall survival between the groups might be explained, suggest the authors, by the additional treatments started after the conclusion of the study, confounding the results. In CRYSTAL, after completion of the study, approximately two-thirds of patients in each group received subsequent chemotherapy, and 25.4% of patients in the FOLFIRI group and 6.2% in the cetuximab-FOLFIRI group received EGFR antibody therapy. "Adding cetuximab to FOLFIRI increased the rate of resection of metastases, but whether this increase improves the potential for cure or long-term survival is unknown," they add.

■ Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. E Van Cutsem, C Kohne, E Hitre et al. *N Engl J Med* 2 April 2009, 360:1408–1417

Combining temozolomide with radiotherapy increases survival in glioblastoma

➜ Lancet Oncology

Updated results of the European Organisation for Research and Treatment of Cancer, and the National Cancer Institute of Canada (EORTC–NCIC) study on glioblastoma show that the survival advantage of combining temozolomide with radiotherapy, compared to radiotherapy alone, is maintained at five years. Nevertheless, most patients successfully treated with the combined therapy eventually had tumour recurrence and died.

For more than three decades postoperative radiotherapy has been the standard treatment for newly diagnosed glioblastoma. Overall survival, however, remains poor, with almost no long-term survivors. In 2004, a joint EORTC– NCIC randomised trial showed that the addition of temozolomide to standard postoperative radiotherapy improved median survival and two-year survival relative to postoperative radiotherapy alone. The study went on to show that patients whose tumour had a methylated promoter for the gene encoding O-6-methylguanine-DNA methyltransferase (MGMT) were more likely to benefit from the addition of temozolomide. It was unclear, however, whether the survival advantage seen at the time of the initial analysis would persist with time.

In the current update, researchers headed by Roger Stupp, from the University of Lausanne in Switzerland, present the five-year results of the phase III study, which involved 573 patients from 85 institutions in 15 countries, who had been randomly assigned to receive radiotherapy alone (*n*=286) or radiotherapy and adjuvant temozolomide (*n*=287).

At the time of final analysis, 532 (93%) of 573 patients enrolled in the study had died after a median follow-up of 61 months (range 11 days to 79 months). Results show

that at the end of five years of follow-up, 9.8% of patients receiving the combined therapy remained alive, compared with 1.9% of those receiving radiation alone. This gave a hazard ratio for death of 0.6, with a 95% confidence interval from 0.53 to 0.75, which was significant at $P<0.0001$.

The benefit of the combined therapy was visible in all clinical prognostic subgroups, including patients aged 60 to 70, the investigators found. But the strongest predictor for outcome and benefit from temozolomide chemotherapy was inactivation of the promoter for the gene encoding MGMT, they said. Patients whose tumours had the inactive promoter showed significantly better survival, with a hazard ratio for death of 0.49, with a 95% confidence interval from 0.32 to 0.76, which was significant at $P=0.001$.

Additional results for the overall group show that, at two years, overall survival was 27.2% with temozolomide versus 10.9% with radiotherapy alone, at three years, overall survival was 16% with temozolomide versus 4.4% with radiotherapy alone, and at four years, overall survival was 12.1% with temozolomide versus 3% with radiotherapy.

Even though the survival advantage of combined treatment was lasting, the researchers write, most patients successfully treated with combined therapy eventually had tumour recurrence and died.

"Survival ... favours combined treatment, which supports the conclusion that the addition of chemotherapy early in the disease course and concomitantly with radiotherapy is the best strategy to incorporate new drugs," write the authors, adding that they have identified the first marker in brain tumours that allows selection of patients who will benefit most from treatment with temozolomide and radiotherapy.

Analysis of recurrence, they add, showed no difference between initial radiotherapy alone and the combined treatment, which supports the hypothesis that the combined therapy might effectively reduce tumour bulk and aggressiveness, but does not modify the disease course. "Many patients with glioblastoma survive for several years. However, true long-term survival and cure are not possible," they said.

Further research is needed, and ongoing trials are investigating the addition of other treatments to the combination of temozolomide plus radiotherapy. These include studies with angiogenesis inhibitors, inhibitors of epidermal growth factor receptors or integrins. "Until better treatments are available, radiotherapy with concomitant and adjuvant chemotherapy is the current standard of care," conclude the authors.

■ Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC–NCIC trial. R Stupp, ME Hegi, WP Mason et al. *Lancet Oncol* May 2009, 10:459–466

BMI predicts metastasis to lymph nodes in pancreatic adenocarcinoma

➜ Archives of Surgery

Obese patients with pancreatic adenocarcinoma who have a body mass index (BMI) greater than 35 are more likely to have metastasis to regional lymph nodes and have an increased risk of cancer recurrence and decreased overall survival according to a recent American study. The authors suggest that, in pancreatic cancer, extreme obesity may be exerting an adverse influence on tumour biology.

Epidemiologic and cohort studies have shown an increased incidence of pancreatic cancer in obese people, while obesity has also been associated with decreased survival in patients with pancreatic adenocarcinoma. However, comparatively little research has been undertaken looking at the relationship of obesity to postoperative morbidity and mortality in patients undergoing surgery for adenocarcinoma of the pancreas.

In the current study, Jason Fleming and colleagues from MD Anderson Cancer Center (Houston, Texas) and the University of Colorado (Denver) examined the influence of obesity, as measured by BMI (calculated as weight in kilograms divided by height in metres squared), on pathology and survival after pancreatectomy for adenocarcinoma.

Using MD Anderson's pancreatic cancer database, the team identified 285 consecutive patients who underwent potentially curative resection for pancreatic adenocarcinoma between January 1999 and October 2006. Clinicopathological data were obtained directly from the institutional database, while BMI was obtained from electronic medical records.

For the purposes of statistical analysis, subjects were divided into five BMI groups, separated into the quartiles: below 23, 23–25, 26–29, and over 30, with the top group further split between 30–35 and above 35 to separate patients with class I obesity from those with class II and class III. In addition to BMI, measured variables included age, length of hospital stay, time of surgery, estimated blood loss, the occurrence of major postoperative complications, tumour size, pathologic margin status, presence or absence of lymph node metastasis and administration of preoperative and postoperative therapy.

Using logistic regression, the team found that patients with a BMI greater than 35 were 16.5 times more likely to have at least one positive lymph node compared with patients who had a BMI of 35 or less ($P=0.007$). After adjusting for the use of preoperative therapy, patients with a BMI of more than 35 still had approximately 12 times the risk of having positive lymph nodes compared with patients with a BMI of 35 or less ($P=0.02$).

Cancer recurrence was observed in 95% of patients (19 of 20) in the group with a BMI greater than 35 versus 61% (161 of 264) of all other patients ($P=0.005$). Additionally,

patients with a BMI of more than 35 were at nearly double the risk of death compared with those with a BMI of 35 or less (P=0.02), and at the last follow-up, 15 of 20 patients (75%) in the group with a BMI of more than 35 had died, versus 137 out of 265 patients (52%) with a BMI of 35 or less.

The authors say that the study extends previous epidemiologic studies by showing that the increased relative risk of death from pancreatic cancer in patients with a BMI greater than 35 includes those patients who undergo surgery to treat pancreatic cancer. "Our findings... suggest that obesity is a host factor affecting tumor biology independent of the difficulties involved in delivering oncologic care in obese patients," they add.

Limitations of the study, write the authors, include the fact that they did not have complete data on lifestyle risk factors (such as alcohol consumption or smoking) and other medical comorbidities that might have contributed to morbidity and death. Future investigations, they add, should include a search for systemic or tumour biomarkers in this group of patients that could provide additional insights.

■ Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma. J Fleming, R Gonzalez, M Petzel et al. *Arch Surg* March 2009 144:216–221

Combining CA-125 and ultrasound shows promise for ovarian cancer screening

➜ Lancet Oncology

Combining the cancer antigen 125 (CA-125) blood test with the transvaginal ultrasound may prove to be an effective screening strategy for ovarian cancer in its earliest and most treatable stages, according to the first interim report from the United Kingdom Collaborative Trial of Ovarian Cancer Screening.

Ovarian cancer is known to have a poor prognosis, with women commonly diagnosed with stage III/IV disease, for which five-year survival rates are around 27% and 16% respectively. Over the past two decades, efforts have been underway to develop early detection strategies using serum CA-125 and ultrasound. Recent refinements to screening have included the introduction of transvaginal ultrasound, improvements in the interpretation of ultrasound findings using morphology-based indices, and the development of a risk of ovarian cancer algorithm to interpret serial CA-125 results.

In the current study, Ian Jacobs and Usha Menon from University College (London, UK) and colleagues analysed data from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) which, between 2001 and 2005, enrolled 202,638 postmenopausal women aged 50–74 years, from 27 regional primary care trusts across the UK. In the study 50,640 women were randomised to multimodal screening (MMS) by blood test and transvaginal ultrasound (transabdominal scans were used when this was not acceptable to the participants), 50,639 were screened by ultrasound alone (USS), and 101,359 were controls who received no screening. Women with abnormal screens had repeat tests; those with persistent abnormalities on repeat screens underwent clinical evaluation and, where appropriate, surgery.

Results showed that screening programmes using MMS were able to detect 90% of women who developed ovarian cancer (34 out of 38), while screening programmes that used USS were able to detect 75% (24 out of 32 cases). The fact that almost half of the cancers were detected in stages I or II (48% of these in stage I) is encouraging, the authors add, since currently only about 28% of invasive cancers are detected at this early stage in most series of ovarian cancer screening.

Overall, the total number of cancer cases detected (87 primary ovarian and three fallopian tube cancers) in the screening groups was similar: 42 in the MMS group and 45 in the USS group. The correct identification of true negatives, however, was significantly better in the MMS, resulting in fewer repeat tests and almost nine times fewer operations per cancer detected.

The results of the UKCTOCS show that both screening strategies are feasible, conclude the authors. "There are inherent differences between the two strategies being tested, with a more subjective element inherent in the ultrasound-based strategy than with the CA125 test, for which it is easy to implement stringent quality control," write the authors.

In an accompanying editorial, Ignace Vergote from Katholieke Universiteit (Leuven, Belgium) and colleagues write that the authors are to be congratulated on the size of the study. "However, to draw any conclusions about the effect of ovarian-cancer screening on mortality we need to be able to compare the mortality rates in the screening groups with the mortality rate in the control group, and these data are not yet available."

They add that the UKCTOCS trial serum bank of over 350,000 samples is likely to be a valuable resource for research on new molecular markers to detect early-stage ovarian cancer. "We feel that this research will be necessary, since data from the prevalence screen of the UKCTOCS trial and other screening trials have not yet convinced us that the time has come to screen for ovarian carcinoma in women without a familial history of ovarian and breast cancer," they conclude.

■ Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). U Mason, A Gentry-Maharaj, R Hallett et al. *Lancet Oncol* April 2009, 10:327–340

■ Screening for ovarian carcinoma: not quite there yet. I Vergote, F Amant, L Ameye et al. *ibid* pp 308–309

Low literacy presents barrier to informed consent

→ Journal of Clinical Oncology

Limited comprehension of prostate cancer terminology and low literacy levels are barriers to informed consent, according to the results of a study focusing on African-American patients with prostate cancer. The study shows that many words used in clinical settings are not well understood by low-literacy populations, highlighting the need to educate caregivers to use non-medical language when discussing prostate cancer.

Research has established that the burden of prostate cancer is greater among African-American men than white men, with African-American men suffering approximately 1.7 times higher incidence and 2.4 times increased mortality than white men. Although underlying reasons for this disparity are not well understood, postulated factors have included racial variations in diet, genetics, biology, socioeconomic status and access to care.

Since prostate cancer disproportionately affects African-American men, Kerry Kilbridge and colleagues, from Massachusetts General Hospital, in Boston, conducted structured interviews to evaluate the comprehension of standard medical terms used in prostate cancer that were found in patient education materials, to obtain informed consent, and to measure outcomes after prostate cancer treatment. Altogether, the team interviewed 105 men, aged at least 40 years, who were predominantly African-American, and who attended one of two general medical clinics in low-income areas.

The men's average household income was US $16,000 (€12,341), 51% were uninsured or had Medicaid, 65% had not completed high school and 27% were either illiterate or read at third grade level or lower. Additionally, just 20% of the study population were able to calculate both a fraction and a percentage.

Testing showed the words 'impotent' and 'erection' were understood by less than 50% of subjects, that 32% knew the term 'vaginal intercourse', 62% knew the word 'rectum' and 23% understood the term 'rectal urgency'. While the word 'urine' was understood by 70% of men, and 79% knew the term 'urination', less than 50% knew the terms 'urinary frequency' and 'urinary function' and just 5% of participants knew the word 'incontinence'. Understanding of terms was significantly associated with reading level.

Seventy-eight percent of men could not anatomically identify the prostate and 35% could not identify the bladder. Although 87% of men had heard of the prostate, just 59% could name something that goes wrong with it, and only 4% could describe its function.

"Our investigation revealed that widespread assumptions made in medical settings about the language for genitourinary function, reading skills, maths skills, prostate cancer knowledge, and anatomic knowledge were inaccurate among patients in our study population," conclude the authors.

Much like a foreign language, they add, the results show that patients may understand a particular term relatively well, but have greater difficulties with compound terms or related terms derived from the same word root. They give the example that subjects understood the word 'intercourse' but found it harder to understand the compound term 'vaginal intercourse'.

The question, they say, is how to apply these research findings to improve prostate cancer communication among underserved men. Using data derived from their research interviews, the investigators constructed a table of 'synonymous colloquial terms' for the common medical words used for prostate cancer, which they are now using in a "process comparable to translation" of English to a foreign language. Introducing a "partially tailored script", which begins by asking the patient to choose the words for urinary, bowel and sexual function that he understands most easily, the interviewer then selects these terms in the computer programme, which automatically substitutes the chosen colloquial terms for the standard medical language.

The process allows the programme to create a "partially tailored quality-of-life instrument" that can be read aloud by the interviewer. The investigators now plan to test such adapted quality-of-life measures among low-income prostate cancer survivors of all races.

In addition, the investigators urge caregivers not to assume that patients have a working knowledge of their internal anatomy and organ systems. "A safer place to start teaching prostate cancer is based on what a patient sees in the mirror. We can explain anatomy stepwise, by teaching new structures in relation to external landmarks that every patient will know regardless of education," they write.

One of the limitations of the study, they add, is that it is not clear how generalisable their findings were outside their sample size from two clinics in a single geographic region.

In an accompanying editorial, Melissa Simon and Robert Lurie from North Western University (Chicago, Illinois) write that it is only by incorporating knowledge of low literacy into the "entire gamut of prostate cancer care and investigation", from informed consent to outcome measures, that "the state of our research will be most representative of all of our patients and thus most translatable from bench to the true bedside."

■ Lack of comprehension of common prostate cancer terms in an underserved population. K Kilbridge, G Fraser, M Krahn et al. *J Clin Oncol* 20 April 2009, 27:2015–2021

■ Heeding our words: complexities of research among low-literacy populations. M Simon, R Lurie, *ibid* pp 1938–1940