NEWSROUND

Selected reports edited by Janet Fricker

Genetic prediction of response to cetuximab

→ Journal of Clinical Oncology

The effect of cetuximab on genes involved in tumour proliferation and inflammation could be used to predict the response of rectal cancer to cetuximab-based chemoradiotherapy (CRT), suggests a Belgian study.

Preoperative CRT with a capecitabine regimen followed by total mesorectal excision is considered the standard treatment for stage II and III rectal cancer, decreasing local relapse rate and improving clinical outcomes. Cetuximab – a chimeric immunoglobulin (Ig) G1 monoclonal antibody directed against the epidermal growth factor receptor (EGFR) – has demonstrated significant clinical activity in metastatic colorectal cancer.

Annelies Debucquoy and colleagues, from the University Hospital Gasthuisberg, in Leuven, Belgium, postulated that the addition of cetuximab to a preoperative concurrent radiotherapy and capecitabine regimen in patients with rectal cancer would improve pathologic response and clinical outcomes.

They set out to characterise the molecular pathways modified by cetuximab-based CRT in patients with rectal cancer, and tried to identify the molecular profiles and biomarkers that might improve patient selection for such treatments. Biomarkers were analysed for associations with pathological response and disease-free survival.

In the phase I/II study, 41 patients with rectal cancer (T3-4 and/or with-positive lymph nodes) received preoperative radiotherapy (1.8 Gy, 5 days/wk, 45 Gy) in combination with capecitabine and cetuximab (400 mg/m^2 as initial dose, 1 week before CRT, followed by 250 mg/m^2/wk for 5 weeks) between November 2004 and June 2006. Tumour biopsies and blood were taken at three time points: at baseline; after the initial dose of cetuximab but before the start of CRT; and at the time of surgery. Proteomics and microarrays were used to monitor the molecular response to cetuximab and identify the profiles and biomarkers that predict treatment efficacy.

The microarray analysis identified 16 genes as significantly influenced by cetuximab (P<0.0005). Of these, three were involved in proliferation (*PIK3R1, CGREF1, PLAGL1*), and three others were involved in tumour invasion (*SERPINE2, TNS4, S100A6*). Furthermore, Ki67 staining to measure changes in tumour proliferation showed a decrease in median expression from 85% to 67% (P=0.0002) after the loading dose of cetuximab; whereas EGFR expression was upregulated in 55% of cases, downregulated in 30% (10 of 33), and remained unchanged in 15% (5 of 33).

The investigators found that disease-free survival was better if the initial dose of cetuximab upregulated EGFR in the tumour (P=0.02) or if there were fibro-inflammatory changes in the resected specimen (P=0.03).

Proteomic analysis showed that changes in expression of six proteins after the cetuximab initial dose (IgM, IL-4, tumour necrosis factor, adiponectin, growth hormone, and thrombopoietin) could predict the occurrence of local recurrences and/or distant metastases with an accuracy of 83.3%, a sensitivity of 50%, and a specificity of 93%.

Furthermore, in patients with recurrences, growth hormone, IgM, thrombopoietin, and TNF were upregulated, and IL-4 was downregulated. Prediction analysis of microarray data (PAM) identified a subset of genes before (50 genes) and after (40 genes) cetuximab administration that characterised patient groups with different relapse potentials.

"In conclusion, our work identified potential molecular pathways involved in cetuximab response in patients with colorectal cancer that should be investigated further to determine their ability to predict clinical outcome in a laboratory-driven larger randomized trial," write the authors, adding that future trials should be designed to combine cetuximab with radiotherapy alone or administer cetuximab after CRT rather than before CRT to avoid its antiproliferative effects interfering with outcome.

■ Molecular response to cetuximab and efficacy of preoperative cetuximab-based chemoradiation in rectal cancer. A Debucquoy, K Haustermans, A Daemen, et al. *J Clin Oncol* 10 June 2009, 27: 2751–2757

Standard regimen better than capecitabine in older women with early breast cancer

➜ New England Journal of Medicine

Women aged over 65 with early-stage breast cancer do better with standard chemotherapy than the oral drug capecitabine, a study from the Cancer and Leukemia Group B (CALGB) Statistical Center has concluded. The study showed patients taking capecitabine had almost twice the risk of relapse or death compared with those receiving older combination regimens.

Capecitabine has been shown to have substantial anti-tumour activity in metastatic breast cancer, with response rates of approximately 30%. In one small, randomised trial involving women with metastatic breast cancer, activity of capecitabine was similar to that of paclitaxel or cyclophosphamide, methotrexate, and fluorouracil (CMF), making it a potential alternative to standard adjuvant chemotherapy.

Lead researcher Hyman Muss, from the University of North Carolina at Chapel Hill, recognised that older women with breast cancer have been under-represented in clinical trials, and data on the effects of adjuvant chemotherapy in such patients are scant. Furthermore, he felt that patients often prefer oral to intravenous chemotherapy, and that an effective oral agent for adjuvant treatment would represent an important advance for treating older women with breast cancer.

In the CALGB study, 633 women with stage I, II, IIIA, or IIIB breast cancer were randomly assigned to standard chemotherapy (*n*=326) or to capecitabine (*n*=307). Standard chemotherapy could either be doxorubicin plus cyclophosphamide (*n*=184), or CMF (*n*=133), according to choices made at the discretion of the patient or her physician. Nine subjects withdrew before choosing a regimen.

As the benefits of improvements in chemotherapy were largely limited to patients with oestrogen-receptor-negative tumours and positive lymph nodes, the investigators undertook an additional unplanned *post hoc* analysis to compare the efficacy of capecitabine with that of standard chemotherapy in patients with hormone-receptor-positive tumours and hormone-receptor-negative tumours.

The trial was stopped after enrolment of the 600th patient, following an interim analysis which showed that capecitabine was likely to prove inferior to conventional regimens with longer follow-up.

Results showed that with follow-up for one year beyond enrolment of the last patient, patients randomised to capecitabine had a hazard ratio for recurrence or death of 2.09 versus conventional therapy (95%CI 1.38–3.17, *P*<0.001). Capecitabine-treated patients had a mortality hazard ratio of 1.85 versus standard adjuvant therapy (*P*=0.02).

The three-year relapse-free survival was 68% with capecitabine and 85% for women assigned to standard therapy. Overall survival was 86% with capecitabine and 91% with standard chemotherapy.

Standard therapy, however, was associated with almost twice the incidence of moderate-to-severe toxicity (64% vs 33%).

The unplanned *post hoc* analysis showed that, among patients with hormone-receptor-negative tumours who received capecitabine, the risk of relapse was more than quadrupled (HR 4.39, 95%CI 2.9–6.7; *P*<0.001), and the risk of death was more than tripled (HR 3.76, 95%CI 2.23–6.34; *P*<0.001), as compared with patients in all other study groups combined.

"This trial shows that standard adjuvant chemotherapy with either CMF or doxorubicin plus cyclophosphamide is superior to capecitabine in older women with early-stage breast cancer," write the authors, adding that the benefits of standard chemotherapy were most pronounced in women with hormone-receptor-negative tumours.

For treatment of older patients, they say, the choice of chemotherapeutic agents, dose, schedule and dose modification should be based on treatment plans in published reports. "Our data are part of a developing body of evidence that the choice of adjuvant chemotherapy really matters in older women with breast cancer, and that standard chemotherapy is superior to the oral agent capecitabine," they write.

■ Adjuvant chemotherapy in older women with early-stage breast cancer. HB Muss, DA Berry, CT Cirrincione et al. *N Engl J Med* 14 May 2009, 360:2055–2065

Multidrug chemotherapy increases secondary cancers in children

➜ JNCI

Survivors of childhood cancer carry a persistent excess risk of developing a second primary cancer throughout their lives, a Scandinavian study has found. Furthermore, modern, multidrug chemotherapy regimens used for many childhood cancers increase rates of secondary neoplasms.

Earlier studies have already established that the risk of suffering a second primary cancer is higher after treatment in childhood compared with that of the general population. Follow-up, however, has been restricted to a few decades following the primary cancer; the pattern of cancer in long-term survivors of childhood cancers has never been investigated comprehensively.

In the current study, Jørgen Olsen and colleagues, from the Institute of Cancer Epidemiology (Danish Cancer Society, Copenhagen), studied a cohort of 47,697 people diagnosed with cancer between 1943 and 2005. Participants, who had all been diagnosed before the age of 20, were identified from the country-wide cancer registries of Denmark, Finland, Iceland, Norway and Sweden. The cohort was stratified into children diagnosed with a first primary cancer between 1943 and 1959 (*n*=5,720); those diagnosed between 1960 and 1974 (*n*=13,254) and those diagnosed between 1975 and 2005 (*n*=28,723).

Results showed that a total of 1,180 second primary cancers were observed in 1,088 people. On the basis of age-adjusted cancer incidence statistics, only 356 cancer cases would have been expected in the general population, yielding an overall standardised incidence ratio for childhood cancer survivors of 3.3 (95%CI 3.1–3.5).

The relative risk was increased by a statistically significant amount in all age groups, even for cohort members approaching 70 years of age. The excess absolute risk for a second primary cancer among survivors increased gradually from one additional case per 1,000 person-years of observation in early life to six additional cases per 1,000 person-years in the age group 60–69 years.

The cumulative risks for a second cancer occurring before the age of 50 years were lowest (8.6%) in the 1943 to 1959 cohort (the pre-chemotherapy era), and higher in both the 1960 to 1974 cohort (first-generation chemotherapy era), at 12.2%, and in the 1975 to 2005 cohort (the combination era), at 13.3%.

Second malignancies were most common in the brain, accounting for 28% of all secondary cancers. Other relatively common sites for second malignancies included skin (13% of cases, including melanoma and nonmelanoma tumours), digestive organs and breast (10% each), bone marrow and lymphatic system (8%), and connective tissue (6%). In all these cases, the standardised incidence ratio was greater than 5.

"This study quantified long-term temporal patterns of increased risk of cancer at specific sites in survivors of childhood cancer," the authors write, adding that the results could be used in the screening and care of these individuals.

"The relative risk for a second cancer remained statistically significantly increased during the age range of 0–69 years, suggesting that the carcinogenic effects of treatment for childhood cancer persist throughout life," conclude the authors. "The extent of the relative increase diminished as patients became older; however, this reduction appeared to be a consequence of the age-dependent increase in background rates (unrelated to radiation treatment or chemotherapy), rather than a moderation of the carcinogenic effect associated with treatment for childhood cancer."

The authors comment that the age-specific relative risk estimates for a second cancer changed over the calendar period of initial treatment, with the highest risk being observed for children treated during the most recent treatment period, 1975–2005, when intensive multiple-agent chemotherapy was introduced. "This increase in relative risk occurred despite the clear advances in radiation treatment during the 1970s and 1980s, including replacement of orthovoltage by megavoltage radiation, which markedly reduced the radiation doses during treatment," write the authors, adding that such trends suggest chemotherapeutic agents play a role in the aetiology of second primary cancers in survivors, either as independent risk factors for second malignancies or by enhancing the carcinogenic effect of radiation.

The authors add that usefulness of the Nordic cancer registry is limited by information on the treatment variables, with the existing information being too crude to allow for meaningful analyses linking type and dose of chemotherapy and radiation with site-specific cancers.

■ Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. JH Olsen, Tl Möller, H Anderson et al. *J Natl Cancer Inst* 2 June 2009, 101:806–813

Pain is still undertreated in many cancer patients

➜ British Journal of Cancer

Most patients with advanced or metastatic cancer experience pain, reports an Italian study, indicating that recourse to WHO third-level drugs is delayed in a substantial number of patients.

Although clinical experience suggests cancer pain can be controlled in up to 90 % of cases, and cancer pain management guidelines have been published since 1986, undertreatment is estimated to affect up to 82% of patients.

In 2006 Giovanni Apolone and colleagues, from the Mario Negri Institute in Milan, Italy, launched an outcome research study to describe the pain characteristics of a large cohort of cancer patients. The study set out to estimate the quality of analgesic drug regimens across different settings, with forthcoming studies planned, to describe longitudinal changes of therapeutic and outcome variables and compare effectiveness of different analgesic strategies.

For the current study, the investigators used the pain management index (PMI) – a standardised measure comparing the most potent analgesic prescribed for individual patients against reported levels of the worst pain experienced by that patient. Potency of the pain killers was determined using a scale based on the WHO analgesic ladder – with 0 indicating no analgesic drug, 1 a non-opioid drug, 2 a weak opioid, and 3 a strong opioid. Levels of pain were determined using the Brief Pain Inventory Score, which assesses intensity of worst, present, least and average pain and pain relief using an 11-point numerical rating scale. The PMI was calculated by subtracting pain levels from analgesic levels, with negative scores considered to indicate undertreatment.

Investigators also identified four specific clinical conditions where there was evidence that pain should be treated with a specific approach according to available guidelines: presence of episodes of breakthrough pain to be treated with a strong opioid as rescue/escape therapy; presence of neuropathic pain to be treated with a specific adjuvant drug; pain with intensity higher than 7 points, calling for a strong opioid as around-the-clock therapy; and presence of bone metastasis to be treated with bisphosphonates. As an additional indicator of the quality of analgesic therapy, the team estimated the proportion of patients in each group who did not receive the recommended therapy.

In the open-label, prospective, non-randomised study, a total of 110 pain centres in Italy recruited 1,801 patients who had been admitted to a pain centre with diagnostic evidence of advanced/metastatic solid tumours and persistent pain related to cancer requiring analgesic treatment. Results show that 61% of patients were receiving a WHO level III opioid, 47% received some kind of rescue/escape therapy and 60% also received some kind of adjuvant analgesic therapy. The percentage of patients achieving negative PMI scores ranged from 44.7% for new patients who had entered the clinic that day, to 8.1% between days 1 and 7, 21.9% between days 8 and 27 and 20.2% after day 27.

For the specific clinical conditions, the prevalence of patients receiving treatment considered inappropriate was 76.2% for breakthrough pain, 23.8% for rescue pain, 55.4% for neuropathic pain, 44.6% for adjuvant pain, 40.9% for worst pain and 59.1% for around-the-clock treatment. The interpretation of the fact that only 38% of patients with bone metastasis were receiving bisphosphonates is less straightforward, write the investigators, as the role of these drugs in obtaining immediate pain relief remains uncertain.

"In summary... the PMI method indicated a high prevalence of analgesic under treatment in Italy, around 50% in some subgroups, which varies according to several factors related to the characteristics of the cases and to some structural and organisation variables," conclude the authors.

The results, they say, support the idea that palliative care, like the prevention and relief of symptoms in cancer patients, needs to be a component of patient care during anticancer treatment, and not merely at the end of life.

"A wider approach is therefore needed, with better education on palliative care and pain management to improve the use of opioids, to standardise the practice of managing cancer pain to minimum standards and to improve the physician–patient communication," write the authors.

Limitations of the study include the fact that selection bias may have occurred, since physicians would have referred only patients who needed expert advice for treating pain to the pain clinic. There are also drawbacks to using PMI as a measure, since it only takes into account one characteristic of pain (the intensity) and the most potent opioid prescribed, but it does not reflect other pain characteristics, opioid titration, routes of administration, patient adherence, rescue and adjuvant therapies or use of non-pharmacological therapies.

■ Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group. G Apolone, O Corli, A Caraceni et al. *Br J Cancer* 12 May 2009, 100:1566–1574

Long-term androgen suppression improves survival in prostate cancer

➜ New England Journal of Medicine

The combination of radiotherapy plus three years of androgen suppression is superior to radiotherapy and six months of androgen suppression in treatment of locally advanced prostate cancer, according to the results of a study by the EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group.

A previous EORTC trial looking at treatment of locally advanced prostate cancer showed that RT plus three years of androgen therapy produced survival benefits compared with radiotherapy. But on the downside, long-term androgen suppression has been shown to reduce quality of life and increase risks of fatal myocardial infarction, fractures and metabolic syndrome.

In the current study, Michel Bolla from the University of Grenoble, France, and EORTC colleagues, set about investigating whether risks might be lowered by replacing long-term androgen suppression with short-term suppression lasting six months, and whether the same overall survival would be obtained. Between 1997 and 2002, 970 men with locally advanced prostate cancer (but nonmetastatic prostate cancer in either T1c to T2a-b clinical stage with pathological nodal stage N1 or N2 or stages T2c to T4 with clinical nodal stages N0 to N2) who had received external-beam radiotherapy plus six months of androgen therapy were randomised to receive no further endocrine suppression treatment (short-term treatment, *n*=483) or to receive 2.5 years of further treatment with a luteinising hormone-releasing hormone agonist (long-term treatment, *n*=487).

After a median follow-up of 6.4 years, a total of 132 patients had died in the short-term group, compared to 98 in the long-term group. Analysed further, the number of deaths due to prostate cancer was 47 in the short-term group, compared to 29 in the long-term group.

The five-year overall mortality was 19% for the short-term group, compared to 15.2% for the long-term group (HR 1.42, 95%CI 15.5–23.0, *P*=0.65 for non-inferiority). But for prostate-specific mortality, the five-year cumulative rate was 4.7% in the short-term group, compared with 3.2% in the long-term group (HR 1.71, 95% CI 1.14–2.57, *P*=0.002). There were no significant differences in the cumulative incidence of fatal cardiac events at five years. After randomisation, there were statistically significant differences in terms of insomnia (*P*=0.006), hot flushes (*P*<0.001) and sexual interest and activity (*P*<0.001) favouring short-term treatment; however, overall quality of life did not differ significantly between the two groups (*P*=0.37).

Differences between short-term and long-term androgen suppression on five-year mortality, write the authors, were modest. "But we believe that the advantage of long-term suppression is likely to be maintained at 10 years, whereas the benefit of short-term suppression may be dissipated by then. We recommend radiotherapy plus long-term androgen suppression for men with locally advanced prostate cancer (classified as stage T2c or above, with a WHO performance status of 0–2) who have no contraindicating coexisting conditions," they conclude.

But in accompanying editorial, Peter Albertsen of the University of Connecticut Health Center (Farmington, Connecticut) says that the study is not applicable to most men with newly diagnosed prostate cancer, since they have smaller tumours and lower grade tumours than those in the trial.

He added that androgen-deprivation therapy for clinically localised disease should be limited primarily to men with advanced localised disease undergoing radiation therapy and to those with clear signs of systemic disease. "These are the patients most likely to benefit from either symptom relief or increased survival that would justify the compromise in quality of life that is associated with androgen-deprivation therapy," he advised.

■ M Bolla, TM de Reike, G Van Tienhoven, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 11 June 2009, 360:2516–2527

■ P Albertsen. Androgen deprivation in prostate cancer – step by step [editorial]. *ibid* pp2572–2574