NEWSROUND

Selected reports edited by Janet Fricker

Low-dose aspirin reduces death from several cancers

→ The Lancet

Daily aspirin reduced deaths due to any cancer by 20%, reports a meta-analysis study, but the benefits only really became apparent after patients had been taking the drug for five years or more.

While earlier studies have suggested that long-term aspirin therapy may protect against colon cancer, the current study led by Peter Rothwell, of the Department of Clinical Neurology at Oxford University, is the first to show that aspirin protects against other cancers, such as oesophageal, gastrointestinal, lung, brain and pancreatic cancers.

Several lines of evidence have suggested that long-term use of aspirin might reduce the risk of some cancers, particularly gastrointestinal tumours. In animal models aspirin reduces incidence or growth rate or both of several cancers, mediated by inhibition of the cyclo-oxygenase enzymes and production of prostaglandins and other inflammatory mediators. Observational studies in humans have also suggested that aspirin reduces the risk of certain cancers. In an earlier study, published in the *Lancet* in October 2010, Rothwell and colleagues showed that long-term low-dose aspirin (75 mg per day) reduced death rates from colorectal cancer by more than a third. In the current research the team studied deaths due to all cancers.

The meta-analysis identified eight randomised trials of daily aspirin versus no aspirin, including 25,570 patients, that had originally been undertaken to look at primary or secondary prevention of vascular events. Doses of aspirin in the eight trials ranged from 75 mg to 500 mg per day. Altogether 674 patients died from cancer in the course of the studies.

Results showed that during the period of the clinical trials, which lasted for about four years, allocation to the aspirin group reduced the risk of death from cancer by 21% (P=0.003).

On analysis of individual patient data, available from seven trials involving 23,535 patients, it became apparent that benefits increased with time. After five years the risk of all cancers was reduced by 34% (P=0.003) and the risk of gastrointestinal cancers by 54% (P=0.003).

The researchers also wanted to determine whether the benefits from aspirin continued over time, and this was made possible by the three UK-based trials that had continued to obtain data for deaths due to cancer after completion of the trials via the national death certification and cancer registration systems.

At 20 years follow-up the three trials showed that the risk of cancer death remained 20% lower for all solid cancers (P<0.0001) and 35% lower for gastrointestinal cancers (P<0.0001) among the participants taking aspirin. When the fall in risk of death was broken down according to individual types of cancer, it was 60% for oesophageal cancers, 40% for colorectal cancer, 30% for lung cancer and 10% for prostate cancer. Reductions in pancreatic, stomach and brain cancers were difficult to quantify due to the small number of deaths. Taking larger doses of aspirin and smoking and gender had no effect on the results.

The authors, from Oxford, Edinburgh and Japan, conclude, "These findings provide the first proof in man that aspirin reduces deaths due to several common cancers. Benefit was consistent across the different trial populations, suggesting that the findings are likely to be generalisable."

When weighing up the risk and benefits of taking aspirin, they add, clinicians will now need to consider the protective effects against cancer. "Although the reduction in risk of

ischaemic vascular events on aspirin in healthy individuals is partly offset by a small increase in risk of non-fatal bleeding complications, the balance of risk and benefit will now be altered by the reduction in cancer deaths after five years' treatment. Our analyses show that taking aspirin daily for 5 to 10 years would reduce all-cause mortality (including any fatal bleeds) during that time by about 10%."

Limitations of the study, write the authors, include the fact that it only used trials of daily aspirin, that too few women had been recruited to allow the investigators to determine the effects of aspirin on gynaecological cancers, and that they were unable to determine the effect of continued aspirin use after 20 years.

The next step, say the authors, will be to explore whether there is any protective effect of aspirin on the incidence or progression of cancer.

■ P Rothwell, F Fowkes, J Belch et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 7 December 2010, doi:10.1016/S0140-6736(10)62110-1

Radiation therapy for head and neck cancer leads to hearing loss

➜ Arch Otolaryngol Head Neck Surg

Patients who have undergone radiotherapy for head and neck cancers experience a higher incidence of hearing loss and more severe hearing handicaps than age-matched controls who do not have cancer, reports a Brazilian study.

Treatments for head and neck cancer, including surgery, chemotherapy and radiotherapy, either alone or in combination, are all known to affect the auditory system and cause temporary or permanent hearing loss. With radiotherapy, when the inner ear is included in the irradiation field, permanent sensorineural hearing loss may result from the loss of ciliated cells in the cochlea, with latency periods ranging from 1.5 to 5 years.

In the current study, Christiane Schultz and colleagues, from the Hospital de Câncer de Barretos (Barretos, Brazil), set out to investigate hearing difficulties among 141 patients with head and neck cancer who had undergone radiotherapy alone or in association with chemotherapy or surgery. The patients, together with 141 age-matched controls (who had never undergone oncological treatment placing their hearing at risk), underwent hearing evaluations and completed the Hearing Handicap Inventory for the Elderly (HHIE) questionnaire, which assessed the effect of hearing loss on their lives. The degree of hearing handicap was divided into three categories according to severity.

Results show that hearing loss was detected in 103 (73.3%) of participants exposed to radiation therapy versus 69 (48.9%) of age-matched controls ($P<0.001$). Severe or profound hearing loss occurred in 6.4% of right ears and 8.5% of left ears in the radiation-treated group, as compared with 0.7% of right ears and 1.4% left ears of control participants.

Hearing loss was mostly sensorineural (resulting from disorders or damage involving the nerves or the inner ear) as opposed to conductive (resulting from interference in sound transmission, usually involving the outer or middle ear).

Furthermore, 19.1% of patients in the radiation treatment group had suffered a severe hearing handicap versus 2.8% in the control group ($P<0.001$). "This indicates that, when present, hearing losses were substantially greater and more incapacitating after the radiotherapy," write the authors.

There was also found to be a correlation between the degree of hearing loss and score on the HHIE questionnaire, with participants whose hearing loss went untreated being more likely to report feeling lonely, depressed, worried, anxious or paranoid, and to have fewer social activities and be less able to process information about their environments.

"This is extremely important because behavioural patterns that are more depressive or that present greater tendencies for social isolation can sometimes be attributed to the cancer or to the functional sequelae of the treatment. Nonetheless, one must remember that hearing loss and hearing handicap may also lead to such behaviour," write the authors.

They conclude that in order to enable better rehabilitation of patients with head and neck cancer, hearing loss should form part of the investigations.

■ S Schultz, M Goffi-Gomez, P Liberman et al. Hearing loss and complaint in patients with head and neck cancer treated with radiotherapy. *Arch Otolaryngol Head Neck Surg* November 2010, 136:1065–1069

Combination therapy shows promise in biliary tract cancer

➜ Lancet Oncology

Cetuximab in combination with gemcitabine and oxaliplatin produced encouraging results as a first-line palliative care treatment in patients with biliary cancer. The Austrian single-centre study found that the addition of cetuximab was associated with increased response, substantial tumour shrinkage and the potential for secondary resection.

Patients with biliary tract cancer have a poor prognosis, with an overall survival that is less than 15% at five years. The only curative treatment is surgical resection, but even after surgical resection recurrence is frequently reported and until recently no standard palliative chemotherapy had been defined. Two phase III trials have recently shown that gemcitabine plus cisplatin (GEMCIS) or oxaliplatin (GEMOX) are superior in terms of overall survival to gemcitabine alone.

The current phase II study by Birgit Gruenberger and colleagues, from Barmherziger Brüder Hospital Vienna, Austria, set out to investigate the efficacy and safety of adding

cetuximab to the GEMOX combination. Cetuximab is a targeted therapy directed against the epithelial growth factor receptor (EGFR), which has been associated with improved outcome for malignancies including colorectal, lung and head and neck cancer.

Between October 2006 and July 2008, 30 patients with unresectable biliary tract cancer were enrolled from one centre in Austria. All patients received 500 mg/m^2 cetuximab as a two-hour intravenous infusion on day 1, and 100 mg/m^2 oxaliplatin on day 2, every two weeks for 12 cycles. The primary outcome was overall response rate.

The investigators found that 19 (63%) of the patients experienced objective response – three (10%) achieved complete response and 16 (53%) achieved partial response. Following major response to therapy, nine patients (30%) were able to undergo secondary curative resection. Of this subgroup, five had intrahepatic cholangiocarcinoma that had initially not been amenable to secondary resection, and four presented with locally advanced extrahepatic tumours that had been unresectable due to vascular involvement. Grade 3 adverse events such as skin rash, peripheral neuropathy and thrombocytopenia occurred in 13 patients, but none reported grade 4 events.

The authors write that comparisons of these results with response rates achieved in other studies verified that cetuximab plus GEMOX has a better overall response rate than gemcitabine alone, GEMOX alone, or other chemotherapy combinations.

Following findings in studies of metastatic colorectal cancer, the association between KRAS mutation status and response to cetuximab was also investigated. KRAS mutations were detected in three out of 30 patients, but did not appear to preclude benefit from combined cetuximab and GEMOX. Patients with KRAS mutated tumours had a shorter median survival than did those with wild-type tumours (1.67 vs 7.67 months, P=0.071).

The authors conclude, "This combination treatment had an acceptable toxicity profile and resulted in potentially curative secondary resection in a third of patients, which significantly lengthened progression-free survival. These findings provide justification for further studies of this treatment combination in a randomised study of a large cohort."

In an accompanying commentary, David Malka, Valérie Bogie and Michel Ducreux, from the Institut Gustave Roussy (Villejuif, France), cautioned that small, single-centre studies can be prone to selection bias, giving the example that 97% of patients in the current study had an Eastern Cooperative Oncology Group performance status of 0–1. Furthermore, they added, several previous reports have found KRAS mutation rates in biliary cancers to be higher than recorded in the current study. "Hence, data from large prospective cohorts are needed to specify the actual prevalence of KRAS mutations – and BRAF mutations . . . and establish whether these mutations are predictive for inefficacy of anti-EGFR antibodies in patients with advanced biliary cancers."

■ B Gruenberger, J Schueller, U Heubrandtner et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* December 2010, 11:1142–1148

■ D Malka, V Boige and M Ducreux. Biliary cancers, chemotherapy, and cetuximab. *ibid* pp 1110–1111

New standard of care defined in multiple myeloma

→ The Lancet

The addition of bortezomib to standard induction therapy (thalidomide plus dexamethasone) prior to double autologous stem cell transplantation in patients with newly diagnosed multiple myeloma improved the rate of complete or near-complete response almost three fold, a landmark study from the GIMEMA Myeloma Network has found. The researchers, led by Michele Cavo from the University of Bologna, Italy, concluded that triple therapy induction represents a new standard of care for patients with multiple myeloma eligible for transplant.

Thalidomide, bortezomib and lenalidomide have greatly advanced myeloma treatment during the past decade, with the thalidomide plus dexamethasone induction regimen (TD) showing the highest activity and being acknowledged as the new standard of care for induction therapy in the US. However, small studies have suggested that the addition of bortezomib to TD (VTD) may result in increased rates of high-quality responses for all phases of myeloma.

Cavo and colleagues undertook a phase III study to assess the efficacy and safety of VTD versus TD as induction therapy in preparation for double autologous stem-cell transplantation in newly diagnosed multiple myeloma patients. Altogether 480 patients aged 18 to 65 from 73 sites in Italy with previously untreated symptomatic myeloma were randomly assigned to receive VTD (n=241) or TD (n=239). The intention to treat analysis included 236 patients in the VTD arm and 238 in the TD arm.

Results showed that 31% of patients in the VTD arm achieved complete or near-complete response compared with 11% of patients in the TD arm (P<0.0001). Furthermore, the median time to best complete response was 9 months in the VTD arm versus 14 months in the TD arm (P<0.0001).

Patients in the VTD arm had a 29% three-year probability of progression or relapse compared with 39% for patients in the TD arm (P=0.0061).

However, on the down side, 56% (n=132) of patients in the VTD arm experienced grade 3 or 4 adverse events compared with 33% (n=79) in the TD arm (P<0.000). Additionally, 10% of patients on VTD experienced peripheral neuropathy compared with 2% on TD (P=0.0004). The study showed no significant differences in stem-cell collection between the two arms.

Despite the high levels of peripheral neuropathy, only one patient experienced grade 4

peripheral neuropathy and only two patients discontinued treatment due to toxic effects.

"Induction therapy with VTD was associated with a significantly higher rate of complete or near complete response than was induction therapy with TD. Therefore, VTD represents a new standard of care to maximise the degree and speed of tumour reduction in patients with myeloma who are eligible for transplant," conclude the authors.

Commenting on the finding that no difference in overall survival was found between the two groups, the authors speculate that the follow-up period may have been too short to detect differences, that the sample size may have been too small and that the increasing availability of effective treatments at time of relapse may have confounded any meaningful analysis of studies in first-line treatment.

In an accompanying commentary, Paul Richardson, from Harvard Medical School, writes, "The unprecedented high quality of responses engendered by these combinations with a generally favourable safety profile bodes well for continued benefit to patients, with yet further improvements in outcome still needed for this otherwise incurable malignancy."

The significant neurotoxicity encountered with VTD, he adds, contrasts with an "otherwise promising picture". Strategies to reduce toxicity include use of less neurotoxic but active combinations of drugs such as lenalidomide and dexamethasone, or lowering doses of bortezomib and thalidomide.

The question of whether additional drugs should be added to the three-drug induction strategy (such as monoclonal antibodies, histone deacetylase inhibitors, heat shock protein-90 inhibitors) also requires further consideration, Richardson writes.

A study is currently underway by the European Myeloma Network to address whether novel agents might delay or challenge the need for autologous stem cell transplantation in myeloma.

■ M Cavo, P Tacchhetti, F Patriarca et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 18 December 2010, 376:2075–2085

■ P Richardson. A new standard of care in newly diagnosed multiple myeloma. *ibid* pp 2043–2044

Docetaxel sets new standard of care in operable, high-risk node-negative breast cancer

➜ New England Journal of Medicine

For women with operable, high-risk node-negative, early-stage breast cancer, adjuvant treatment with the drug combination of docetaxel, doxorubicin and cyclophosphamide (TAC) reduced the risk of recurrence by 32% compared with the traditional treatment approach of fluorouracil, doxorubicin and cyclophosphamide (FAC), reports a study from the Spanish Breast Cancer Research Group (GEICAM).

"Our findings… show that TAC is effective both in patients with node-positive and in those with high-risk node-negative early-stage breast cancer," write the authors, led by Miguel Martin from the Hospital General Universitario Gregorio Marañón in Madrid.

Although adjuvant taxane-based regimens are now the standard of care for patients with node-positive early-stage breast cancer, their efficacy in patients with high-risk node-negative disease has not been defined. The benefits of adjuvant chemotherapy in the node-negative populations have, however, been well established.

In the open-label phase III GEICAM 9805 study, between June 1999 and March 2003, 1060 women with axillary-node-negative breast cancer and at least one high-risk factor for recurrence were randomised to treatment with either TAC (n=539) or FAC (n=521) for six cycles every three weeks, following surgery. The study was funded by Sanofi-Aventis (makers of docetaxel) and involved 40 centres in Spain, four in Germany and two in Poland.

Results show that at a median follow-up of 77 months, 87.8% of the women were alive and disease-free in the TAC group compared to 81.8% in the FAC group (HR 0.68, 95% CI 0.49–0.93; P=0.01). The benefit was consistent across subgroups regardless of hormone receptor status, HER2 status, menopausal status, age, tumour size or histologic grade. On the basis of the trial, the number of patients who would need to be treated to prevent recurrence in one patient is 17, write the authors.

The difference in survival – 95.2% for TAC and 93.5% for FAC – was not significant (HR 0.76; 95% CI 0.45–1.26; P=0.29). This, the authors suggest, was because the number of deaths was small (26 vs 34). The rates of grade 3 or 4 adverse events were 28.2% with TAC and 17.0% with FAC (P<0.0001), and serious adverse events were recorded in 4.7% of the women in the TAC group compared to 0.8% in the FAC group.

"The small number of deaths occurring at the time of the analysis indicates that a longer follow-up period will be needed to assess survival among patients with node-negative breast cancer as compared with those who have node-positive disease," write the authors.

"The GEICAM 9805 trial shows the effectiveness of an adjuvant taxane-based regimen over a non-taxane-based regimen in a population of patients with axillary, lymph-node-negative, early-stage breast cancer," they conclude, adding that the acute toxic effects associated with TAC are manageable when treatment is combined with granulocyte colony-stimulating factor introduced as primary prophylaxis.

The benefit of TAC over FAC in premenopausal women, speculate the authors, may be partly due to its ability to induce amenorrhoea in more women.

■ M Martín, M Seguí, A Antó et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. *NEJM* 2 December 2010, 363:2200–2210