NEWSROUND

Selected reports edited by Hannah Brown

Patients 'should welcome' rash from EGFR inhibitors

→ Clinical Cancer Research

Development of an itchy pustular rash over the torso, head and face of patients treated with inhibitors of the epidermal growth factor receptor (EGFR) – a type of targeted drug that is increasingly used to treat several types of cancer – may actually indicate the treatment is working well, according to a recently published analysis of two phase III trials. According to the study, the worse the rash is the more likely patients are to survive their cancers or at least maintain good control of the disease. Researchers from OSI Pharmaceuticals, the company that manufactures the EGFR inhibitor erlotinib (Tarceva), analysed side-effect data and outcomes from two phase III studies that showed a positive result after treatment with their drug, which is just one of many similar agents currently being prescribed by oncologists.

Both trials from which the researchers drew their data had made a special note of a rash among patients who had received the drug and those who had not – and it is this information the researchers used to asses a link between severity of the rash and effectiveness of the treatment. The first trial compared treatment with 150 mg erlotinib daily with placebo in 731 patients with stage IIIB/IV non-small-cell lung cancer who had failed at least one prior chemotherapy regimen. Overall survival, tumour response, progression-free survival, and time to symptom deterioration were all improved in the group taking erlotinib. The second study evaluated erlotinib plus gemcitabine compared with placebo plus gemcitabine for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. Erlotinib again improved survival. Most of the patients taking erlotinib in both studies developed a post-treatment rash, which was graded for severity by the clinical trial teams. The OSI investigators excluded from their analysis all patients who had died within 28 days of therapy, because they reasoned that this time frame was not sufficient for a rash associated with outcome to have developed. This specific cut-off was chosen because there was a large difference in the incidence of rash among those who died within four weeks and those who survived longer (<20% vs >70%).

In the first study, 81% of the 444 erlotinib-treated patients experienced a rash. Patients who developed grade 1 rash survived 144% longer than patients who did not develop rash, and patients with grade 2 rash survived 245% longer than patients who did not develop rash. In the other study, among the 254 patients in the erlotinib plus gemcitabine group the incidence of rash was 71%. But in the second study the incidence of rash among the placebo group was, at 30%, almost double that in the first trial. As a result, there were no statistically significant differences in outcomes between the patients with rash and those without. The authors explain the discrepancy between the two studies by explaining that their analysis of the correlation of rash with outcomes in the second study was potentially confounded because rash is an adverse event associated with both erlotinib and gemcitabine treatment.

Concluding that "the patient who does not develop a characteristic rash within 2 to 4 weeks is less likely to benefit from erlotinib," the researchers note that physicians and patients should view the development of rash as a desirable outcome – perhaps as a sign of erlotinib-induced biological effect. They emphasise the need to develop methods for managing the rash without interfering with the improvement in outcomes it brings. "Optimal management of rash in patients on EGFR inhibitors remains somewhat controversial, but aggressive treatment of the side-effects may allow patients to continue receiving therapy without dose interruption or drug discontinuation," they write. As part of the clinical management of this side-effect, patients should also be counselled to help them regard the development of the rash as a positive step, the researchers suggest.

■ Correlation between Development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. B Wacker, T Nagrani et al. *Clin Cancer Res* 1 July 2007, 13: 3913–3921

More evidence for the surgical learning curve

→ JNCI

Patients with prostate cancer who are operated on by surgeons who have done more than 250 radical prostatectomies – an operation involving complete removal of the prostate gland – are much more likely to avoid recurrence of disease than those operated on by less experienced surgeons, according to a study published in the *Journal of the National Cancer Institute*.

Researchers from the Memorial Sloan-Kettering Cancer Center in New York analysed outcome data from 7,765 patients who had radical prostatectomies done by 72 surgeons at four institutions between 1987 and 2003. The researchers quantified the surgeons' experience by the number of times they had performed the procedure before each operation, and adjusted for case mix to assess the effect of surgical technique and skill on outcomes.

The patients were assigned to one of five groups according to the experience of their surgeon at the time of their operation: <50, 50–99, 100–249, 250–999, or ≥1000 prior radical prostatectomies. Follow-up consisted of measuring serum levels of prostate specific antigen (PSA) every 3–4 months during the first year after surgery, and less frequently in subsequent years. Cancer recurrence was defined as a serum PSA of more than 0.4 ng/ml followed by a subsequent higher PSA level.

More surgical experience was associated with a greater likelihood that the patient's cancer would not return after their operation. The learning curve for this procedure was very steep; there was dramatic improvement in patient outcomes as surgeons' experience increased up to 250 operations, after which increasing experience had little influence on cancer recurrence. Patients treated by inexperienced surgeons (for example, those with 10 prior operations) were nearly 70% more likely to have evidence of recurrence of their prostate cancer within five years than those whose surgeons had performed 250 operations.

"Our findings also have implications for education in surgical oncology," say the authors. "Although the successful practice of surgery necessarily presumes a lifetime of learning, the large number of cases required before the learning curve plateaus suggests the need to expand opportunities for training in surgical technique for surgeons in the early years after residency training."

■ The Surgical learning curve for prostate cancer control after radical prostatectomy. AJ Vickers, FJ Bianco, AM Serio et al. *J Natl Cancer Inst* 1 August 2007, 99:1171–1177

High-dose chemotherapy for refractory testicular cancer

→ New England Journal of Medicine

Patients with advanced testicular cancers whose disease has progressed despite receiving standard chemotherapy can be cured by additional drug therapy at very high doses, according to a recently published retrospective case series.

The vast majority of men who develop testicular cancer are cured of their disease by the standard chemotherapy regimen, which involves multiple courses of cisplatin. However, for the small proportion who do not respond to this treatment, other options must be sought. For most patients, these options include salvage chemotherapy with cisplatin plus ifosfamide plus vinblastine or paclitaxel for four courses, or high-dose chemotherapy with autologous haematopoietic stem-cell transplantation to rescue the bone marrow from the myeloablative effects of chemotherapy.

Reporting a series of patients who were treated at Indiana University, Lawrence Einhorn and colleagues recalled 10 years' experience with the latter option. Between February 1996 and December 2004, 184 patients were treated with carboplatin chemotherapy at five times the dosage administered to men receiving initial therapy, followed by peripheral-blood stem-cell rescue.

During a median follow-up of 48 months, 116 of the patients (63%) were continuously disease free. Of these 116 patients, 104 (90%) were disease-free for more than two years. Six additional patients had complete remission of disease, four after receiving paclitaxel plus gemcitabine and two after undergoing subsequent resection of a germ-cell tumour. The toxic effects of high-dose chemotherapy were primarily myelosuppression, mucositis, nausea, vomiting, dehydration, peripheral neuropathy and hearing abnormalities. There were three sudden drug-related deaths; two were due to hepatic failure, and one was due to pulmonary toxic effects.

The authors conclude that, "There should be little or no debate on the use of high-dose chemotherapy for a patient with a germ-cell tumor that is refractory to platinum-based chemotherapy or that is not cured by a cisplatin–ifosfamide regimen as salvage chemotherapy. In our study, 18 of 40 patients with progressive metastatic disease and tumors that were refractory to platinum remained disease-free for a median of 49 months (range, 22 to 110), and 22 of 49 patients who received high-dose chemotherapy as third-line or later therapy remained disease-free for a median of 46 months (range, 25 to 112)."

■ High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. LH Einhorn, SD Williams, A Chamness et al. *New Engl J Med* 26 July 2007, 357: 340–348

FDA: tomato consumption does not decrease cancer risk

→ JNCI

There is only limited evidence for an association between eating tomatoes and a decreased risk of certain cancers, according to an article published in the *Journal of the National Cancer Institute*.

Several studies have reported an association between the consumption of tomatoes or

lycopene, an antioxidant that gives tomatoes their red colour, and a decreased risk of some cancers, particularly prostate cancer. But before foods and dietary supplements can be sold in the US with such claims on their packaging, the US Food and Drug Administration (FDA) must review and approve these claims based on the available scientific evidence.

Reviewing their deliberations about the anti-cancer properties of tomatoes and lycopene, FDA panel member Claudine Kavanaugh and colleagues found no evidence that tomatoes reduced the risk of lung, colorectal, breast, cervical or endometrial cancer. However, there was very limited evidence for associations between tomato consumption and reduced risk of prostate, ovarian, gastric and pancreatic cancers. Based on this assessment, the FDA decided to allow qualified health claims for a very limited association between tomatoes and these four cancers. Their analysis found no credible evidence that lycopene, either in food or in a dietary supplement, was associated with reduced risk of any of the cancers evaluated. For prostate cancer, for example, the FDA issued this statement: "Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer. [The] FDA concludes that there is little scientific evidence supporting this claim."

In an accompanying editorial, Paul Coates, of the National Institutes of Health, says the limited number of clinical trials available made the FDA's decision a hard one. "However," he says this lack of data does not diminish "the importance of using evidence-based review principles to evaluate important diet–health relationships." He added, "It may be argued that evaluating a diet–health relationship is precisely the circumstance in which systematic review techniques can be most appropriate and effective, because they are transparent and objective, and the search and review strategies could be exactly reproduced by others."

■ The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. CJ Kavanaugh, PR Trumbo, KC Ellwood. *J Natl Cancer Inst* 18 July 2007, 99:1074–1085

■ Evidence-based reviews in support of health policy decisions (editorial). PM Coates. ibid p 1059

Taking lapatinib with food could increase effective dose and save money

➔ Journal of Clinical Oncology

Encouraging patients to ignore prescribing advice and take the targeted drug lapatinib with food could increase the effective dose by five times, thereby reducing the cost of treatment, argue Mark Ratain and Ezra Cohen from the University of Chicago in the *Journal of Clinical Oncology*. They add, however, that studies of this suggestion are needed before it should be considered standard practice.

Current prescribing notes for lapatinib, a drug that inhibits both the epidermal growth factor receptor and another tyrosine kinase called ERBB2, say patients should take the tablet at least an hour before food or wait until an hour afterwards – because those were the conditions under which the drug was tested, and they form the basis of its approval for market. However, Ratain and Cohen claim that pharmacokinetic data on the bioavailability of lapatinib show that food significantly increases the concentration of the drug in the body. What is more, if the meal is high in fat, the concentration of the drug is further increased. As a result, 500 mg of lapatinib taken with food may be as effective as taking the currently approved 1,250 mg without food.

Lapatinib was approved by the FDA in March of this year for women with advanced HER2-positive breast cancer. The FDA approved the 1,250 mg dose of lapatinib based on a large phase III clinical trial demonstrating its effectiveness and safety at that dose without food. The dose is taken as five 250 mg tablets on an empty stomach, and costs $2,900 (€2,050) per month. However, applying Ratain and Cohen's rationale could lead to cost savings of 60% or $1,740 (€1,250). "As we enter an era of 'targeted' anticancer agents, with a monthly cost measured in the thousands of dollars, we should view drug–drug or drug–food interactions as opportunities to lower costs," they write. However, the authors strongly emphasise that a formal pharmacokinetic study of a lower dose of lapatinib with food would be needed to confirm these findings before any change in dosage could be considered safe and effective.

■ The value meal: how to save $1700 per month or more on lapatinib.MJ Ratain, EE Cohen. *J Clin Oncol* 10 August 2007, 25:3397–3398

Lymphoedema is inversely associated with node status

➔ Annals of Surgery

Lymphoedema following surgery or radiotherapy for breast cancer may be determined by factors that pre-date the treatment, according to a recent study.

Breast-cancer related lymphoedema – swelling of the arm accompanied by feelings of discomfort and heaviness – occurs in women who are treated with surgery or radiotherapy to the lymph nodes under the arm, although only some women suffer from the condition. The cause is poorly understood, but it is generally assumed that treatment in some way impairs lymphatic drainage and by doing so causes the arm to swell. In this study, researchers pooled data from two studies looking at the relationship between axillary lymph-node dissection and lymphoedema. In all, data on 212 patients who had undergone surgery to their underarm lymph nodes, but no radiotherapy to this area, were analysed. Assessments of the extent of arm swelling were done by taking the circumference of the arm at 4 cm intervals from the wrist and, from those measurements, an estimate of arm volume was calculated. Measurements were taken both pre- and postoperatively at several pre-specified time points. Average arm volume changes were then compared between patients with positive nodes and those with no evidence

of tumour spread. The researchers also investigated trends in arm volume changes according to the number of positive nodes.

Positive node status (i.e., evidence of tumour in one or more of the dissected lymph nodes) was significantly associated with swelling in the lower arm in study 1 and for both studies combined. Adjusted for tumour size, time since operation, and repeated measures, arm volume excess was reduced with increasing numbers of positive nodes, a finding that was significant in study 1 and in both studies combined.

Although a number of previous studies have suggested a relationship between lymph-node positivity and lymphoedema, many of them are affected by the confounding effect of axilliary radiotherapy on lymphoedema. This study addressed that problem. The results are counterintuitive to current understanding of the pathophysiology of lymphoedema, which implies surgery and/or radiotherapy are the cause, say the authors. "Our results suggest that while these treatments bring on the condition, its severity or extent is determined by other factors that predate the therapy," they conclude.

■ Lymph node status and breast cancer-related lymphedema. AD Purushotham, TM Bennett Britton, MB Klevesath. *Ann Surg* July 2007, 246:42–45

Xerostomia must be prevented to improve quality of life

➔ Int J Radiat Oncol Biol Phys

Detrimental effects of the common radiation-induced side effect of xerostomia – dryness of the mouth caused by damage to the salivary glands – increase over time and severely impact on the quality of life for patients with head and neck cancer, according to a recent study.

Xerostomia is the most frequently reported late side-effect of radiotherapy. Late side effects are generally considered irreversible and progressive and are, therefore, of substantial importance in determining patients' quality of life. But information about the clinical relevance of radiation-induced toxicity in terms of quality of life is scarce. Therefore, Dr Jellema and colleagues decided to investigate the impact of xerostomia on quality of life among head and neck cancer patients treated with primary radiotherapy.

Between December 1998 and January 2004, 288 patients with head and neck cancer were recruited to the study. All had a life expectancy of at least 12 months and all had received radiotherapy as a first-line treatment, with curative intent. Acute and late radiation-induced morbidity were assessed according to the Radiation Therapy Oncology Group criteria, first at six weeks, and then at six-monthly intervals. Patients were also assessed at these appointments using a cancer-specific quality-of-life questionnaire. Xerostomia was found to have a significant effect on different dimensions of quality of life, an effect that was more pronounced in female and younger patients. Moreover, the effect of xerostomia on overall quality-of-life outcome increases with elapsing time, even though the incidence of xerostomia decreases.

This is the first study investigating the impact of radiation-induced xerostomia on overall quality of life and, although some publications suggest that xerostomia may recover over time in some patients, it appears from these findings that for most the damage induced by radiation is permanent. These results, conclude the authors, underline the need to prevent the development of radiation-induced xerostomia.

■ Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. AP Jellema, BJ Slotman, P Doornaert. *Int J Radiat Oncol Biol Phys* 1 November 2007, 69:751–760

Exercise may improve adherence to adjuvant chemotherapy

➔ Journal of Clinical Oncology

Encouraging patients who are undergoing adjuvant chemotherapy for breast cancer to take either aerobic or resistance exercise might increase the chance that they will complete a full course of chemotherapy, according to the surprise findings of a recent study.

Adjuvant chemotherapy improves the chances of long-term survival, but also tends to cause fatigue and worsen physical functioning. The Canadian START trial – Supervised Trial of Aerobic versus Resistance Training – aimed to investigate whether exercise may improve the quality of life of patients on adjuvant chemotherapy. It examined the independent effects of aerobic and resistance exercise on quality of life, fatigue, psychosocial functioning, physical fitness, body composition and chemotherapy completion rates, along with side-effects.

The researchers recruited 242 patients with stage I–IIIA breast cancer who were just beginning their first-line adjuvant chemotherapy, and randomly assigned them to one of three groups: usual care (n=82), supervised resistance exercise (n=82) or supervised aerobic exercise (n=78). All completed a questionnaire, physical fitness test, and a bone mineral density scan at the time of enrolment.

The researchers found that neither resistance nor aerobic exercise significantly improved quality of life – something the researchers attributed, in part, to the wide variability in quality of life change scores among the patients on chemotherapy. But they observed that undertaking exercise seemed to contribute to improved self-esteem among trial participants and, surprisingly, to the chemotherapy completion rate.

Self-esteem was superior in both the exercise groups compared with usual care and the chemotherapy completion rate, as measured by relative dose intensity, was higher in both exercise groups: 78% and 74% of patients undertaking resistance and aerobic exercise, respectively, received 85% of their planned dose, compared with just 66% in the usual care group.

■ Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. KS Courneya, RJ Segal, JR Mackey, et al. *J Clin Oncol*, published online 4 September 2007, doi:10.1200/JCO.2006.08.2024