NEWSROUND

Selected reports edited by Janet Fricker

Cetuximab rash is a good sign in head and neck cancer

➜ Lancet Oncology

For patients with locoregionally advanced squamous-cell carcinoma of the head and neck (SCCHN), the latest five-year overall survival data confirm that radiotherapy plus cetuximab is better than radiotherapy alone. Furthermore, the US investigators found that cetuximab-treated patients with a prominent cetuximab-induced rash (grade 2 or above) had more than 2.5 times longer overall survival than patients exhibiting no rash or mild rash.

In 1998, James Bonner and colleagues from the University of Alabama (Birmingham, Alabama) designed a randomised trial investigating the value of adding cetuximab to radiotherapy in 424 patients with locally advanced SCCHN. Results at three years showed that survival was 55% among those randomised to cetuximab and radiation compared to 45% for those randomised to radiotherapy alone. Of particular interest to the investigators were several studies across multiple cancers (including colorectal, non-small-cell lung cancer and pancreatic cancer) suggesting a correlation between overall survival and presence of a cetuximab-induced acne-like rash.

In the current paper, Bonner and colleagues report the five-year survival data and investigate the relationship between cetuximab-induced rash and survival. Patients with locally advanced SCCHN of the oropharynx, hypopharynx or larynx with measurable disease were randomly allocated in a 1:1 ratio to receive either comprehensive head and neck radiotherapy alone for six to seven weeks (n=211) or radiotherapy plus weekly doses of cetuximab (400 mg/m^2 initial dose, followed by seven weekly doses at 250 mg/m^2, n=213).

Results show that median overall survival at five years was 36.4% in the radiotherapy-alone group versus 45.6% in the cetuximab/radiotherapy arm (HR 0.73, 95% CI 0.56–0.95; P=0.018). The median overall survival in the radiotherapy-alone group was 29.3 months (95% CI 20.6–41.4) compared with 49.0 months (32.8–69.5) in the cetuximab group.

As expected, patients randomised to cetuximab experienced a greater number of grade 3 and 4 infusion reactions than those who received radiotherapy alone. Of the patients who received cetuximab, those with a prominent cetuximab-induced acneiform rash (grade 2–4) had a 68.8-month median overall survival compared with 25.6 months (HR 0.49, 95% CI 0.34-0.72, P=0.002) in those who developed mild or no rash (grade 0–1). The small number of patients in the radiotherapy-alone group who developed acneiform rashes showed no survival difference compared with patients not exhibiting rash.

"These updated survival results provide further support for considering the combination of cetuximab and radiotherapy as a standard option in the treatment of locally advanced SCCHN," write the authors, adding that their previous report provided the impetus for the inclusion of cetuximab and radiotherapy as a treatment option for locally advanced SCCHN in the 2007 National Comprehensive Cancer Network (NCCN) guidelines.

It is possible, add the authors, that the acneiform rash is a biomarker of an immunological response conducive to optimal outcomes. "In the future, the presence or absence of a cetuximab-induced rash [might be used] to identify patients who benefit from more prolonged treatment with cetuximab or treatment with other agents," write the authors, adding that further work will be necessary to determine the mechanistic significance of the acneiform rash.

In an accompanying editorial, Kevin Harrington, from the Institute of Cancer Research (London, England), writes, "The relatively rapid onset of skin reactions (>75% exhibited the rash within two weeks) seems to offer the prospect of making decisions to continue or stop cetuximab after the first few weeks of treatment."

He adds that the National Cancer Institute Common Toxicity Criteria were used to define the boundary between mild rash (grade 1) and prominent rash (grade 2). "This discrimination rests on the absence (grade 1) or

presence (grade 2) of symptoms, rather than an objective measure of the rash. Therefore, the reliability of this measure must be confirmed in future studies."

He comments too on the implications of recent studies showing important survival differences between SCCHNs that were associated with the human papillomavirus (HPV) and those that were not. While the importance of ensuring balance in human papillomavirus (HPV) status between the treatment groups could not have been anticipated when the study was conceived, writes Harrington, the better prognosis of patients with HPV-positive locally advanced SCCHN means that HPV status must be included as a stratification factor in future studies.

■ A Bonner, P M Harari, J Giralt et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* January 2010, 11:21–28

■ KJ Harrington. Rash conclusions from a phase 3 study of cetuximab [editorial]. *ibid* pp 2–3

Abbreviated radiotherapy effective for breast cancer

➜ New England Journal of Medicine

An intense three-week course of radiation therapy was found to be just as effective as the standard five-week regimen for women with early-stage breast cancer, report Canadian researchers.

In women with breast cancer who undergo breast-conserving surgery, whole-breast irradiation reduces the risk of local recurrence and can prevent the need for mastectomy. Radiobiologic models have suggested that a larger daily dose of radiation (hypofraction), given over a shorter time (accelerated therapy) might prove just as effective as standard treatment, consisting of 50.0 Gy of radiation given in 25 fractions over a period of five weeks in daily fractions. Such an abbreviated regimen would offer the advantage of being both more convenient for patients and less resource intensive than standard schedules.

In 2002 Tim Whelan, from the Michael G DeGroote School of Medicine at McMaster University, Hamilton, Ontario, reported the five-year results of a randomised clinical trial comparing abbreviated radiation with the standard approach. At the time, local recurrence rates were the same (3%) for both groups, and cosmetic outcomes (reflecting the radiation-related morbidity) were also similar. "Nevertheless, because radiation-related microvascular damage increases over time, there was concern that late toxic effects of radiation associated with the hypofractionated regimen could develop," write the authors, who in the current study report their findings at a median follow-up of 12 years.

Between 1993 and 1996 the investigators recruited women with invasive breast cancer who had undergone breast-conserving surgery with negative axillary lymph nodes who were randomised to either standard whole-breast irradiation (50 Gy given in 25 fractions over a period of 35 days, n=612) or accelerated hypofractionated irradiation (42.5 Gy given in 16 fractions over a period of 22 days, n=622).

Results at 10 years showed that the risk for local recurrence was 6.7% among the standard-treatment group and 6.2% among women in the hypofractionated-treatment group (absolute difference, 0.5 percentage points; 95% CI –2.5 to 3.5).

There were 126 deaths in the standard-treatment group and 122 in the hypofractionated-treatment group (P=0.79).

At 10 years, 71.3% of the women in the standard-treatment group and 69.8% in the hypofractionated-treatment group had good or excellent cosmetic outcomes (absolute difference, 1.5 percentage points; 95% CI –6.9 to 9.8).

Although there was a worsening of the cosmetic outcome over time, say the authors, which coincided with the increase in toxic effects of irradiation of the skin and subcutaneous tissue, there was no increase in toxic effects in women who received accelerated hypofractionated radiation therapy as compared to those who received standard therapy.

"Our long-term results provide support for the use of accelerated, hypofractionated, whole-breast irradiation in selected women with node-negative breast cancer after breast conserving surgery," write the authors, adding that such an approach was both more convenient and less costly than standard treatment. "Its availability as a treatment option may lead to an increase in the number of women who receive breast irradiation after breast conserving surgery."

Potential limitations, write the authors, were that the trial was restricted to women who had node-negative, invasive breast cancer. For this reason the results are not applicable to patients for whom nodal irradiation is planned. Furthermore, women with large breasts were not included, and few women received adjuvant chemotherapy – a treatment that may place them at increased risk for adverse cosmetic outcome with standard radiotherapy. "So it is unclear whether hypofractionation would lead to an outcome that would be any worse than that with standard treatment," write the authors.

■ T Whelan, J P Pignol, M Levine et al. Long-term results of hypofractionated radiation therapy for breast cancer. *NEJM* 11 February 2010, 362:513–520

Adding MRI to breast cancer assessment does not cut reoperations

➜ The Lancet

The addition of MRI scans to conventional triple assessment techniques for the diagnosis of breast cancer has no effect on the reoperation rate, reports the UK COMICE trial.

The COmparative effectiveness of Magnetic resonance Imaging in breast CancEr (COMICE) trial was the first randomised trial to assess whether contrast-enhanced MRI in women with primary breast cancer scheduled

for wide local excisions decreased their need for reoperations. The COMICE trial was inspired by observational studies showing greater accuracy for MRI than for X-ray mammography or ultrasound (*JCO* 17:110–119). It is known that around 20% of women return to surgery for 'reoperation' because their tumour has not been completely removed. The COMICE investigators hoped that by better delineating the extent of the tumours the 'reoperation' rate would be minimised.

Lindsay Turnball and colleagues, from the Centre for Magnetic Resonance Investigations at Hull Royal Infirmary (Hull, England), recruited 1623 women aged 18 years or older with biopsy-proven breast cancer from 45 centres in the UK. In addition to receiving triple assessment (defined as clinical examination, imaging of the breast by X-ray mammography and/or ultrasound, and pathological assessment of the lump by fine-needle aspiration cytology or core biopsy) women were randomised to receive MRI (*n*=816) or no further imaging (*n*=807). The primary endpoint of the study was the proportion of patients undergoing a repeat operation or further mastectomy within six months of randomisation, or a pathologically avoidable mastectomy at initial operation.

Results show that 19% of women (*n*=153) needed reoperation in the group that received MRI in addition to conventional triple assessment, compared with 19% (*n*=156) in the group that did not receive MRI (OR 0.96, 95%CI 0.75–1.24; *P*=0.77).

The researchers also found no differences in health-related quality of life between the groups 12 months after initial surgery, and no significant difference in costs ($8877.36 per MRI patient vs $8402.10 per non-MRI patient; *P*=0.075).

"However, in terms of total costs, results suggested a difference between the two trial groups, with the MRI group costing more than the non-MRI group, although the difference was not statistically significant," write the authors. "In view of the similar clinical and health related quality-of-life outcomes of patients in both groups, we conclude that the addition of MRI to the conventional triple assessment might result in extra use of resources at the initial surgery period, with few or no benefits to saving resources or health outcomes, and the additional burden on patients to attend extra hospital visits."

In an accompanying commentary, Elizabeth Morris, from Sloan-Kettering Cancer Center and Weill Cornell Medical College (New York), said that the COMICE study does not fully answer the question of whether preoperative breast MRI adds benefit, because recurrence and overall survival were not examined. "It is too early to completely dispense with preoperative breast MRI. Importantly, COMICE has shown that preoperative breast MRI might not be for all women and that routine breast MRI in the evaluation of early breast cancer, as managed by those participating in this study, does not decrease reoperation rates."

■ L Turnbull, S Brown, I Harvey et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *The Lancet* 13 February 2010, 375:563–571

■ E Morris. Should we dispense with preoperative breast MRI? *ibid* pp 528–530

Combination chemotherapy no advantage in kidney cancer

➜ The Lancet

Combined treatment with interferon-α2a, interleukin-2, and fluorouracil did not improve overall or progression-free survival compared with single therapy using interferon-α2a alone, found a joint MRC (British Medical Research Council) and EORTC (European Organisation for Research and Treatment of Cancer) study. However, the investigators, led by Martin Gore from the Royal Marsden NHS Trust (London, England), concluded the combined regimen may still have a role to play because it produced remissions of clinically relevant length in some patients.

In metastatic renal cell carcinoma the immunotherapy regimen associated with the highest response rates has been the combination of interferon-α2a, interleukin-2 and fluorouracil, with response rates as high as 39% being reported by Atzpodien and colleagues (*Br J Cancer* 85:1130–1136). Not all groups, however, have been able to reproduce such high response rates. The MRC and EORTC therefore decided to mount a large-scale randomised trial comparing interferon-α2a alone, the then standard of care in Europe, with combined interferon-α2a, interleukin-2 and fluorouracil.

Between April 2001 and August 2006, the RE04/30012 trial, undertaken in 50 centres across the UK, the Netherlands, Slovakia, Germany, Belgium and Denmark, randomly allocated 1066 patients with metastatic renal cancer to treatment with interferon-α2a alone (*n*=502) or treatment with interferon-α2a plus interleukin-2 plus fluorouracil (*n*=504). Treatment was not masked.

Results show that the median overall survival was 18.8 months for patients receiving interferon-α2a versus 18.8 months for combination therapy (HR 1.05, 95%CI 0.90–1.21; *P*=0.55). The absolute difference in overall survival was 0.3% at one year and 2.7% at three years, favouring single-agent interferon-α2a.

The best overall response, however, was significantly higher in patients receiving combined therapy, at 23%, compared with 16% for patients receiving interferon-α2a alone (*P*=0.0045), though this was not nearly as high as that reported by Atzpodien and colleagues.

Not surprisingly, grade 3/4 toxicity was more common among patients receiving the combined therapy (53% vs 36%, *P*<0.0001).

On the basis of these findings, the authors conclude that, "Although combination therapy does not improve overall or progression-free survival compared with interferon-α2a alone, immunotherapy might still have a role because it can produce remissions that are of clinically relevant length in some patients. Identification of patients who will benefit from immunotherapy is crucial."

They note that dose modifications and breaks occurred with both regimens, but that

breaks were more frequent for patients receiving combined therapy than for those receiving interferon-α2a, with three-quarters of patients given interferon-α2a alone receiving 80% or more of their expected dose.

The high degree of dose reduction with combined therapy might provide an explanation for the absence of benefit with this regimen, write the authors. "However, we believe that this finding is representative of the feasibility of this treatment, and no difference existed between the treatments according to size or experience of the treating centre."

The study, they add, might be criticised for limiting the cycles of combination immunotherapy to two, although this decision was taken after wide consultation with major cancer centres where cytokine therapies were used.

In an accompanying editorial, Bernard Escudier from the Gustave Roussy (Villejuif, France) congratulated the MRC RE04/EORTC GU 30012 investigators on undertaking the largest ever trial in mRCC. "They have clearly answered the initial question: the triple regimen was definitively not superior to interferon-α2a and was more toxic. Thus, although the response rate is higher than with interferon, chemoimmunotherapy should no longer be used in mRCC."

The study, he added, emphasises that interferon remains an acceptable option in patients with good-risk features, and that the safety of interferon appears to be better when used by doctors who have wide experience of the drug compared with those who do not. For example, grade 3–4 fatigue occurred in 18% of patients in RE04/30012 study, run in UK and EORTC centres, compared with 30% of patients in the CALGB study in the US.

■ ME Gore, CL Griffin, B Hancock. Interferon alpha-2a versus combination therapy with interferon alpha-2a, interleukin-2, and fluorouracil in patients with untreated metastatic renal cell carcinoma (MRC RE04/EORTC GU 30012): an open-label randomised trial. *The Lancet* 20 February 2010, 375:641–648

■ B Escudier. Chemo-immunotherapy in RCC: the end of a story [editorial]. *ibid* pp 613–614

Molecular profiling predicts Hodgkin's lymphoma outcomes

➜ New England Journal of Medicine

Increased numbers of tumour-associated macrophages are strongly associated with shortened survival for Hodgkin's lymphoma patients, a Canadian study has reported. These latest findings offer a new biomarker for risk stratification, allowing clinicians to predict which patients can be cured with standard treatments and which are more likely to relapse.

Currently most patients receive at least four cycles of polychemotherapy and, if indicated, radiotherapy. Autologous haematopoietic stem-cell transplantation can rescue about 50% of patients in whom primary therapy has failed. Despite advances in treatments for Hodgkin's lymphoma, around 20% of patients still die from progressive disease. None of the prognostic-factor scoring systems currently available are able to identify those patients in whom treatment is likely to fail.

Randy Gascoyne and colleagues, from the British Columbia Cancer Agency (Vancouver, Canada), set out to build "a robust discriminative model" predictive of treatment failure, that might be used to identify a small set of genes that could be used to separate patients into the different outcome groups. The study was undertaken in two stages.

The first stage of the study involved analysing 130 frozen samples obtained from patients with classic Hodgkin's lymphoma during diagnostic lymph-node biopsy for gene expression profiling to determine which cellular signatures correlated with treatment outcome. Primary treatment was defined as a failure if the lymphoma had progressed at any time after the initiation of treatment, while treatment success was defined as the absence of progression or relapse. The second stage involved validating the findings in an independent cohort of patients with immunohistochemical analysis.

Results of the first stage of the study showed that gene-expression profiling identified a gene signature of tumour-associated macrophages that was significantly associated with primary treatment failure (P=0.02).

Of the potential markers identified in the first part, the researchers further analysed CD68+ macrophages, CD20+ B cells, and matrix metalloproteinase-11 (MMP11) by immunohistochemical staining of samples from an independent cohort of 166 patients. CD68, they discovered, "stood out because of its significant correlation" with survival. On a scale of 1 to 3, a score of 3 (representing the highest concentration of CD68+ macrophages) was associated with lower 10-year disease-specific progression-free survival of 59.6%, compared to 88.6% for a score of 1 (P=0.003), as well as an increased likelihood of relapse after stem-cell transplantation (P=0.008).

In patients with limited-stage disease, a CD68 score of 1 was associated with 100% 10-year disease-specific survival (P=0.04).

"Our study showed the value of enumerating CD68+ macrophages in diagnostic lymph-node samples for prediction of the outcome after primary treatment and secondary treatment (in particular, autologous stem-cell transplantation)," write the authors. "The absence of an increased number of CD68+ cells in patients with limited-stage disease defines a subgroup of patients for whom the rate of long-term disease-specific survival is 100% with the use of available treatments."

In an accompanying editorial, Vincent DeVita and José Costa, from the Yale School of Medicine (New Haven, Connecticut), wrote that the technology should enable "the selection of patients with a particularly poor prognosis (regardless of stage) for aggressive treatment, which can bring more logic to the treatment of this curable cancer." Most patients, they add, could be spared a combination of therapies or radiotherapy with attendant long-term toxic effects.

■ C Steidl, T Lee, S Shah. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. *NEJM* 11 March 2010, 362:875–885

■ V DeVita, J Costa. Towards a personalised treatment of Hodgkin's disease [editorial]. *ibid* pp 942–943