Addendum: A separate study has recently been published in which 17 of 21 patients received autologous non-myeloablative haemopoietic stem cell transplants following conditioning with cyclophosphamide and a single 20-mg dose of alemtuzumab.[8] Two of these patients developed grade IV thrombocytopenia at seven and 14 months after transplantation. Rabbit antithymocyte globulin was substituted for alemtuzumab for the last four patients following the adverse report published by the FDA. Although five patients needed a further round of immunosuppression, all 21 patients were free from progression at 37 months and 16 were free from relapses.

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Tailoring treatment with targeted therapies for advanced colorectal cancer

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TITLE 1 KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab

AUTHORS 1 Lièvre A, Bachet J-B, Boige V et al.

JOURNAL 1 *J Clin Oncol* 2008; 26:374–9.

TITLE 2 Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer

AUTHORS 2 Amado RG, Wolf M, Peeters M et al.

JOURNAL 2 *J Clin Oncol* 2008; 26:1626–34.

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SUMMARY

These two complementary papers reflect the emergence of data over the course of 2008 that have changed the use of anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapies. Two monoclonal antibodies directed at the epidermal growth factor receptor are currently licensed for the treatment of advanced colorectal cancer: cetuximab and panitumumab.

Lièvre et al. investigated the prognostic role of KRAS (Kirsten rat sarcoma viral oncogene, which codes for a signalling protein in the EGFR pathway) mutations in the treatment of patients with cetuximab and chemotherapy for advanced colorectal cancer. This was a retrospective study to validate previous work which had suggested that KRAS status could predict response to cetuximab. Mutations in KRAS status were hypothesised to be associated with poorer outcomes. DNA was extracted from frozen or paraffin-embedded colorectal cancer tissue samples from 89 patients and analysed for KRAS mutational status. The patients' clinical responses to cetuximab were assessed on serial computed tomography (CT) scans using internationally recognised response criteria. It was shown that there was a significant association between KRAS mutations and response: none of 24 patients (0%) with KRAS mutations responded to cetuximab, while 25 of 65 patients (39%) who had wild-type (non-mutated) KRAS responded. Pooling the data from the previous study showed similar results (0% vs 44%). This response also translated into improved survival.

Amado et al. reported a retrospective analysis of the KRAS status of 427 patients who had been treated in a phase three clinical trial comparing panitumumab (a fully humanised monoclonal anti-EGFR antibody) with best supportive care. This was a more homogenous group of patients compared with the study above. Seven potential KRAS mutations were assessed. Again, there was a significant association between KRAS mutations and response rate; none of the patients with KRAS mutations

benefited from panitumumab, while 17% of those with wild-type KRAS benefited from panitumumab. KRAS mutations were seen in 43% of patients.

OPINION

Anti-epidermal growth factor receptor expression has not been shown to predict clinical benefit to anti-EGFR antibody therapy.[1] A combination of anti-EGFR monoclonal antibody therapy and chemotherapy with irinotecan is associated with a better response than the antibody alone. Response rates of approximately 20–25% and improvement in survival of three months can be achieved.[1,2] KRAS mutations are found in 30–45% of colorectal cancers.

Patients also have toxicities associated with these agents, such as severe acneiform skin rashes, paronychia, hypomagnesaemia, fatigue and diarrhoea. The development of a skin rash on treatment had previously been shown to be associated with a better clinical outcome.[1] Escalation of the dose of cetuximab to achieve a skin rash has been tried but has been shown to be more beneficial in patients without KRAS mutations.[2]

Trial data that supported these papers were presented at the American Society of Clinical Oncology meeting in June 2008.[2,3] It is now generally accepted that the KRAS status of a colorectal cancer will predict the likelihood of benefit from these monoclonal antibodies. The European Medicines Agency approved panitumumab only for patients with wild-type KRAS. Several ongoing trial protocols have subsequently been rewritten to require KRAS testing prior to randomisation to potential anti-EGFR therapies.

Cetuximab and panitumumab are costly enough drugs to raise questions about their availability for patients. Neither treatment has funding approval for the National Health Service in the UK, from the Scottish Medicines Consortium or the National Institute for Health and Clinical Excellence. The cost of these drugs is also an issue in the US. Being better able to predict who is likely to benefit from these therapies is attractive from the viewpoints of patient toxicity and health economics.

KRAS testing is a step forward in tailoring treatment, but it is likely that there are more pieces to be placed in the jigsaw and that tailoring treatment to individual patients will be more complex and costly than we expect. Technologies to allow this approach are becoming more available. There are already hints that other mutations may help to identify patients who will benefit from targeted therapies and that combinations of targeted therapies may be beneficial.[6]

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Women's lifestyle and venous thromboembolism

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TITLE The relationship between lifestyle factors and venous thromboembolism among women: a report from the MISS study

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SUMMARY

This longitudinal cohort study of 40,000 Swedish women aged 25–64 years assesses lifestyle factors and the risk of venous thromboembolism (VTE). The Melanoma Inquiry of Southern Sweden (MISS) recruited 1,000 women per age year, and followed them prospectively for a mean of 11 years. A total of 39,973 women were selected at