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]

REFERENCES

1 Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Eng J Med* 2004; 351:337–45.

2 Tejpar S, Peeters M, Humblet Y et al. Phase I/II study of cetuximab dose-escalation in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic (PK), Pharmacodynamic (PD) and efficacy data. *J Clin Oncol* 2007; 25(18S):4037.

3 Tejpar S, Peeters M, Humblet Y et al. Relationship of efficacy with KRAS status (wild type versus mutant) in patients with irinotecan-refractory metastatic colorectal cancer (mCRC), treated with irinotecan (q2w) and escalating doses of cetuximab (q1w): the EVEREST experience (preliminary data). *J Clin Oncol* 2008; 26(15S):4001.

4 Van Cutsem E, Lang I, D'haens G et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. *J Clin Oncol* 2008; 26(5S):2.

5 Bokemeyer C, Bondarenko I, Hartmann JT. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: The OPUS experience. *J Clin Oncol* 2008; 26(5S):4000.

6 Di Nicolantonio F, Miriam M, Molinari F et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008; 26:5705–12.

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

random from the general population registry for 1990; 74% (29,518) agreed to participate. Using International Classification of Diseases Codes (ICD 9 and 10), those with VTE, both participants and non-participants, were identified. Sweden's national cause of death register and the national patient register, which record all admissions to hospital, were also interrogated for the same subjects and codes up to 31 December 2002, thereby establishing the number of registered VTEs in those selected. In addition, information on malignancies was gathered from regional and national cancer registries.

Participants completed a questionnaire at recruitment between 1990 and 1992 and a follow-up questionnaire between 2000 and 2002. The questionnaire covered risk factors for melanoma but included questions of interest for thrombotic risk, such as alcohol consumption, parity, sports, smoking, use of combined oral contraceptive (COC), age at menopause and educational level. At the end of the study, questions also included height, weight and physical activity. Definitions for some of these parameters are given in Table 1.

Results showed that sedentary women had twice the risk of VTE as those who were physically active and that heavy smokers had a 30% increased risk compared with non-smokers as did those who were overweight. Those who drank <5 g/day of alcohol had twice the risk of those who drank moderate amounts. A diagnosis of cancer increased the risk of VTE fourfold, and for each additional year of age the risk increased 6%, with a sharper increase above 59 years. Interestingly, the use of COCs during the study did not increase the risk of VTE significantly over never users, but those who were users prior to the study had a 30% reduction in risk compared to never users.

TABLE 1 Definitions of some parameters in the MISS study questionnaire

BMI kg/m²	Cigarettes/ lifetime	Physical activity	Alcohol consumption*
<25	0	None	None
25–30 Overweight	<100,000 Low	Go for a walk ≥1/week	<5 g/day Low
>30 Obese	≥100,000 Heavy	Strenuous exercise	5–10 g/day Moderate/safe
			10–15 g/day Moderate
			>15 g/day Heavy

*150 ml wine (12%) contains approximately 14 g alcohol. Safe limit for women: 14 units/week.

OPINION

Venous thromboembolisms cause significant female morbidity and mortality.[1] Some occur during times of increased risk, such as pregnancy or surgery, and sometimes have an underlying inherited thrombotic tendency. Hormone replacement therapy and COCs are also associated with an increased risk of VTE as are obesity and smoking.[2–5] A reduction of cardiovascular events is associated with light to moderate alcohol consumption (<30 g/day) and exercise, but the influence of these measures on VTE is not known. This study addresses some of these questions in a large cohort of women with rigorous follow-up. This population has a higher incidence of factor V Leiden, a known risk factor, albeit weak, for thrombosis, and will not be representative of all populations of women, but the study provides confirmation of known risk factors and suggests other behaviours that may reduce risk.

The finding that previous users of COCs had a reduced risk of VTE was unexpected. Possibly, previous users who had not had a VTE constituted a lower risk group, while those who had had VTE could take preventative measures at the time of the study.

The strengths of this study lie in the large unselected population and the collection of most data at its commencement. The weaknesses include a lack of detail about VTEs prior to the study, and the lack of or incompleteness of prospective data on body mass index and regular exercise.

It is heartening to see a study identifying risk factors for VTE that does not rely on thrombophilia testing but instead focuses on lifestyle factors, over which individuals have some control. Such factors allowing a reduction of VTE risk in women include a normal weight, regular physical activity and not smoking and are similar to those for reduction of risk of other disease such as cardiovascular disease. It is also heartening to see that a daily glass of wine or equivalent is associated with a lower risk of VTE.

REFERENCES

1 Heit JA, Silverstein MD, Mohr DN et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999; 159(5):445–53.

2 Dahlbäck B. Blood coagulation. *Lancet* 2000; 355(9215):1627–32.

3 Lisman T, de Groot PG, Meijers JC et al. Reduced plasma fibrinolytic potential is a risk factor for venous thrombosis. *Blood* 2005; 105(3):1102–5.

4 Goldhaber SZ, Grodstein F, Stampfer MJ et al. A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997; 277(8):642–5.

5 Hansson PO, Eriksson H, Welin L et al. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: 'the study of men born in 1913'. *Arch Intern Med* 1999; 159(16):1886–90.