

# IN THE THERAPY UPDATE PUBLIC DOMAIN

colorectal cancer

## Cetuximab and bevacizumab have demonstrated exciting new potential for treating metastatic colorectal cancer, reports Liz McElligott, clinical services manager, Parkside Oncology clinic

Each year more than 35,000 new cases of colorectal cancer are recorded in the UK, making it the third commonest malignancy. Early detection and good management result in improved survival rates, yet 44 people still die from the disease every day in the UK. Risk factors for colorectal cancer include age, diet, obesity and genetic factors. Fewer than one in 10 cases are due to an inherited gene defect.

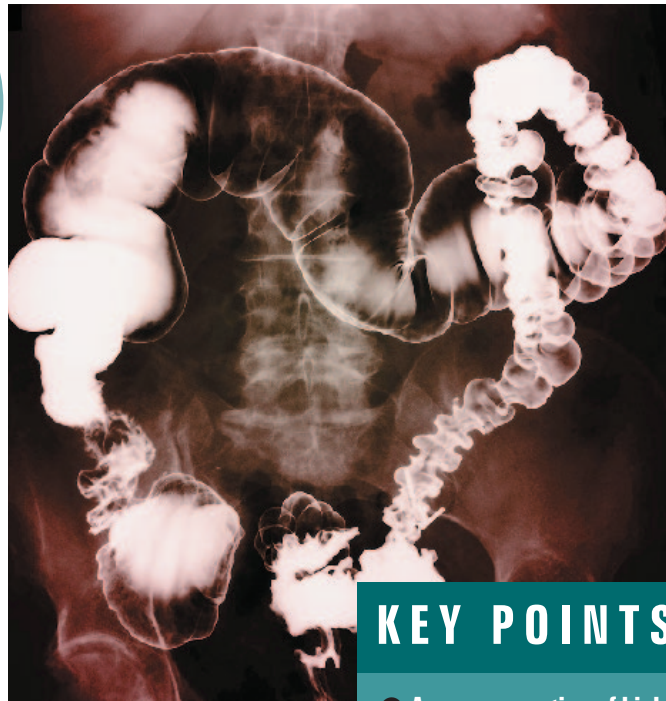
Until about 15 years ago, 5-fluorouracil, first developed in the 1950's, was the first choice treatment for colorectal cancer. The addition of calcium folinate for the treatment of metastatic disease led to this combination being used in the adjuvant setting. The introduction of newer agents, such as oxaliplatin and irinotecan, into the metastatic setting has seen a stepwise increase in median survival from 15 to 19.5 months. In 2003, the first oral chemotherapy for

metastatic colorectal cancer was approved by the National Institute for Clinical Excellence (NICE).

A new generation of biological agents, cetuximab and the most recently licensed bevacizumab, target specific growth pathways and have demonstrated exciting new potential for treating metastatic colorectal cancer. NICE approved both trastuzumab and rituximab for breast cancer and non-Hodgkins lymphoma respectively, in 2002. It is possible that these newer monoclonal antibodies will achieve similar success for colorectal cancer with experience and use over the coming years.

### ADVANCES IN TREATMENT

Colorectal cancer can be managed in a variety of different ways including surgery, radiotherapy, chemotherapy and, more recently, through the use of targeted therapies, which have an entirely different mode of action



to chemotherapy. In 1971, Judah Folkman proposed the innovative hypothesis of developing angiogenesis inhibitors to treat cancer and in 1989, vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, was purified and cloned by Dr Napoleone Ferrara. In 2005 the first anti-angiogenic treatment was licensed and is now available in the UK.

So what role could VEGF and bevacizumab (a recombinant humanised monoclonal antibody to VEGF) have in the treatment of colorectal cancer? The first of its kind, bevacizumab is an anti-angiogenic drug which directly inhibits angiogenesis and also improves the delivery of chemotherapy to the tumour by altering tumour vasculature.

VEGF is a blood circulating protein that activates endothelial cell division when it interacts with the VEGF receptor. It affects the permeability of small blood vessels causing leakage of plasma proteins and the formation of an extravascular fibrin gel, in which endothelial cells grow. A high level of VEGF, which is over-expressed in many cancer cells, stimulates the growth of new blood vessels – essential for tumour growth. VEGF causes the tumour vasculature to become permeable and leaky, resulting in increased interstitial pressure in the tumour and affecting the delivery of nutrients, oxygen and therapeutic agents. Anti-VEGF therapies have the potential to re-

verse these effects and have been a focus of research in tumour anti-angiogenesis, which has led to the development of a neutralising monoclonal antibody.

## KEY POINTS

- A new generation of biological agents show exciting potential for treating metastatic colorectal cancer
- Anti-VEGF therapies have been the focus of research in tumour anti-angiogenesis
- The addition of bevacizumab to chemotherapy increased average survival by nearly five months

verse these effects and have been a focus of research in tumour anti-angiogenesis, which has led to the development of a neutralising monoclonal antibody. Bevacizumab is a humanised monoclonal antibody directed against VEGF. Blocking VEGF stops the growth of new blood vessels to a tumour, as VEGF is an essential protein that makes blood vessels grow. It is the first and only cancer treatment to target VEGF and show survival benefit. Bevacizumab differs from cetuximab, which has a multi-factorial inhibitory effect. Cetuximab is a chimeric monoclonal IgG1 antibody, which binds to the epidermal growth factor receptor thereby causing cell cycle arrest and collaborating to decrease angiogenesis.

### WELL TOLERATED

Phase I and II trials using bevacizumab showed that it is well tolerated in patients with solid tumours, and can be safely combined with doxorubicin, carboplatin/paclitaxel, capecitabine and 5-FU/LV. The main side-effects seen in the trials were bleeding events, thromboembolic events, hypertension and proteinuria. Although manageable, these required specific monitoring and management in subsequent phase III trials.

Evidence of bevacizumab's effectiveness was determined

in a landmark study in which it was shown that the addition of bevacizumab to chemotherapy enabled patients to survive longer, increasing the average survival by nearly five months (20.3 months versus 15.6 months). This is the largest improvement in survival time shown in a phase III trial that can be attributed to the addition of a single targeted therapy to chemotherapy for metastatic colorectal cancer.

There was also an increase in the disease free progression time from 6.2 months in the chemotherapy alone arm to 10.6 months with the addition of bevacizumab. The results of this phase III trial led to bevacizumab

gaining its licence in the UK earlier this year.

### UNDER DEVELOPMENT

A wide range of other drugs that target the VEGF system are currently under development, with promising results being seen with monoclonal antibodies directed at VEGF and small molecule tyrosine kinase inhibitors that block downstream signalling to the membrane-bound tyrosine kinase VEGF receptors. Other approaches to inhibit the VEGF system include ribozymes targeting VEGF receptor-1 mRNA, antibodies directed against the VEGF receptor and a form of soluble VEGF receptor designed to bind and negate the activity of VEGF in the circulation.

Additional trials are underway using bevacizumab as a treatment for other types of metastatic cancer, such as breast and lung cancer. Interim results suggest considerable potential. The combination of monoclonal antibodies, alongside the array of cytotoxic chemotherapy alternatives now available for the treatment of metastatic colorectal cancer, and potentially others, means that many patients will now have the opportunity to benefit, prolonging their survival, while retaining a good quality of life. ●

■ More on monoclonal antibodies on page 22.

**“The addition of bevacizumab to chemotherapy enables patients to survive longer”**

next month: drug misuse