

# Colorectal Cancer

## Managing the therapeutic options

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Colorectal bowel cancer (cancer of the colon and rectum) is the second most common cause of cancer death in England and Wales. Early detection and good management results in improved survival rates. Each year, more than 35,000 new cases of colorectal cancer are recorded in the UK (1) making it the third most common malignancy.

Until about fifteen years ago, 5-fluorouracil (5FU), first developed in the 1950s, was the drug of choice in the treatment of colorectal cancer. The addition of calcium folinate in advanced practice led to this combination being investigated in the adjuvant setting. However, the introduction of newer agents, oxaliplatin, irinotecan and fluoro-pyrimidines, has seen a stepwise increase in median survival ranging from 15 to 19.5 months (2). In 2003, the first oral chemotherapy for advanced bowel cancer was approved by NICE. Further improvement is needed and the addition of biological agents to the current therapies selected is one strategy that may well build on this incremental gain.

A new generation of biological agents, Cetuximab (Erbix(r)) and more recently licensed Bevacizumab (Avastin(r)), target specific growth pathways and have demonstrated exciting new potential for treating metastatic colorectal cancer.

This article will explore colorectal cancer and the role of monoclonal anti-bodies such as Cetuximab and Bevacizumab as treatment options. Bevacizumab is a recombinant humanized monoclonal antibody to Vascular Endothelial Growth Factor (VEGF). The first of its kind, this anti-angiogenic drug directly inhibits angiogenesis and also improves the delivery of chemotherapy by altering tumour vasculature. The epidermal growth factor (EGF) is implicated in malignant angiogenesis, invasion and metastasis and inhibition of apoptosis. The epidermal growth factor receptor (EGFR) is over expressed in a number of solid tumours. Cetuximab binds to EGFR more strongly than EGF, thereby causing cell cycle arrest and inhibition of vascular endothelial growth.

Approximately 55% of patients presenting with bowel cancer

have metastatic disease (3). Bowel cancer is the second biggest cancer killer in the UK with 44 people dying from bowel cancer every day. Current 5-year survival is about 50% (1).

Risk factors for bowel cancer include age, and 90% of people are over the age of 50, although bowel cancer can occur in the younger population. Also being overweight or obese can increase the risk of bowel cancer developing. Less than 1 in 10 cases of bowel cancer are due to an inherited gene defect, although there are certain families who have an increased risk of developing bowel cancer due to a variety of conditions. Having a personal history of bowel cancer or chronic bowel inflammation may also increase the risk of developing bowel cancer.

Bowel cancer can be managed in a variety of different ways including diet, surgery, with about 80% of patients undergoing some form of surgery as part of their disease management. Radiotherapy, using high-energy rays can help in the management of intestinal blockage and pain or bleeding, and chemotherapy, which involves the

use of cytotoxic medicines often used in advanced bowel cancer, improves survival and quality of life.

The most recently available medicines are the targeted therapies, which have an entirely different mode of action to chemotherapy. Molecular cell research has enabled new therapies to be developed. Cetuximab is a chimeric monoclonal IgG1 antibody, which binds to the epidermal growth factor receptor thereby causing cell cycle arrest and decreasing angiogenesis. This treatment is currently available for metastatic colorectal cancer. Cetuximab shrinks tumours by targeting the epithelial growth factor receptors and has a multi-factorial inhibitory effect.

The current license for Cetuximab, first licensed in UK in June 2004, is for the treatment of EGFR expressing colorectal cancer in combination with Irinotecan after Irinotecan failure. Pre-clinical evidence for anti-tumour activity of EGFR blockade was shown by Prewett et al in 2002 (4). More recently, the European "BOND" study compared Cetuximab plus Irinotecan with Cetuximab alone in patients with Irinotecan refractory, EGFR



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expressing colorectal cancer. Median time-to-progression was significantly improved with the addition of Cetuximab from 1.5 months to 4.1 months and a trend was seen for prolonged survival from 6.9 months to 8.6 months (5). COIN, a UK Medical Research Council Phase III trial of 2500 patients, is looking at patients with inoperable metastatic colorectal cancer. The trial involves treatment for 6 months of weekly Cetuximab infusions plus an Oxaliplatin based regimen against standard chemotherapy or intermittent 12-weeks chemotherapy.

In 2005, the first anti-angiogenic treatment Bevacizumab was licensed and is now available in the UK. 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 5

months (20.3 months versus 15.6 months). Also, there was an increase in the disease free progression time from 6.2 months in the chemotherapy alone arm versus 10.6 months with the addition of Bevacizumab (6).

These novel concepts in the medicines portfolio offers a new type of treatment and adds a new dimension to the management of advanced bowel cancer. The use of monoclonal antibodies represents a significant step forward in the treatment of advanced colorectal cancer. Cetuximab and Bevacizumab provide new classes of treatment, which could change the way bowel cancer may be treated in the future. The combination of monoclonal antibodies, alongside the array of cytotoxic chemotherapy alternatives now available for the treatment of this type of cancer, means that many more patients will have the opportunity to benefit, prolonging their survival, from this unique therapy.

## References

1. Cancer Research UK. "Large Bowel Fact Sheet" Feb 2005.
2. Goldberg R, Sargent D, Morton R, et al "Journal of Clinical Oncology 2004"; 22(1):22-33.
3. NICE: "Guidance on Cancer Services Improving Outcomes in Colorectal Cancers Manual Update" May 2004.
4. Prewett MC, Hooper AT, Bassi R, et al "Clinical Cancer Research 2002" 8(5):994-1003.
5. Cunningham D, Humblet Y, Siena S et al "New England Journal of Medicine 2004" 351:337-344.
6. Hurwitz H, Fehrenbacher L, Novotny W, et al Bevacizumab plus Irinotecan, Fluorouracil and Leucovorin for Metastatic Colorectal Cancer, "New England Journal of Medicine 2004" 350(23):2335-2342.