Personal view of the potential role for Cetuximab (Erbitux®) and Bevacizumab (Avastin®) in the treatment of advanced colorectal cancer (aCRC) in UK.

I hold the position of senior lecturer in medical oncology at Leeds University with an honorary consultant position in the Leeds Teaching Hospitals NHS trust. My clinical specialty is gastrointestinal oncology with a significant proportion of patients having colorectal cancer. I have participated in many clinical trials of novel therapies in colorectal cancer including those involving cetuximab and bevacizumab.

Current standard therapy for advanced colorectal cancer in UK

There has been a significant change in the outlook for patients with advanced colorectal cancer (aCRC) over the past decade. The introduction of oxaliplatin (Ox) and irinotecan (Ir) to the only existing active cytotoxic 5-fluorouracil (5FU) significantly improves response rates, progression free and overall survival. Median survival of around 20 months is consistently observed in trials where Ox and Ir along with 5FU are used during therapy. This compares with median OS of around 12 – 15 months with the best 5FU regimens alone.

Uncertainties over how best to use all three active agents have been addressed by a number of recent large randomised trials and meta-analyses (Tournigand 2004; Grothey 2004; Seymour 2005). It would appear that use of 5FU (given by bolus and infusion in combination with leucovorin (LV)), Ox and Ir during the course of treatment gives the greatest likelihood of long term survival. However, differences in sequencing or combination of these drugs during treatment may have less influence on overall survival (OS). Thus a randomised study of 5FU/LV plus either Ox or Ir as first line therapy in aCRC followed by the alternative combination as second line therapy upon disease progression showed no significant difference in median OS. The MRC FOCUS trial has also shown no significant difference in OS between schedules of treatment where fluoropyrimidines were combined with Ox or Ir as 2nd or 3rd line salvage therapies and those where a combination was used as first line therapy.

As a result of all this data it is clear that the optimal treatment of patients with advanced CRC involves use of Ir, Ox and 5FU/LV but decisions on sequencing and combination of treatment are a clinical judgement influenced by patient characteristics and preferences.

Oral fluoropyrimidines (e.g. capecitabine and UFT) are beginning to open up further treatment options for patients by reducing the need for permanent central venous catheters (required for infusional 5FU) with their associated complications and cost implications.

Despite these improvements the majority of patients with aCRC will die of their disease within a couple of years of diagnosis emphasising the continued need for additional active agents for this condition.

Bevacizumab – clinical data and experience

Bevacizumab, a humanised monoclonal antibody against vascular endothelial growth factor (VEGF), has been developed as a rationally designed "targeted" therapy. Such agents are so called as they specifically interact with molecules (the target) that are essential for development or progression of the cancer, VEGF, a pro-angiogenic mitogen, appears to represent a suitable target as it is upregulated in most human cancers including colorectal cancer and increased tumour expression correlates with advanced disease and poor prognosis. Pre-clinical data indicates activity of bevacizumab against colorectal cancer as well as synergism between bevacizumab and cytotoxic chemotherapy.

Although there remain few published trials using bevacizumab in colorectal cancer the evidence that does exist, including that in abstract form, indicates significant improvements in outcome with acceptable additional toxicity. This is supported by similar evidence of benefit in trials of bevacizumab in other cancer types.

The seminal studies in advanced colorectal cancer have combined bevacizumab with bolus 5FU/LV (Roswell Park regimen) and Ir + bolus 5FU/LV (IFL regimen), neither regimen routinely used in the UK. Addition of bevacizumab to IFL (in an 813 patient randomised placebo controlled trial) improved median progression free survival by 4.4 months and overall survival by 4.7 months (Hurwitz 2004). The patient population treated in this trial represented the better end of the spectrum with aCRC (mean age 59yr and 55% having normal performance status). A similar selection bias was observed in a trial of 5FU/LV +/- bevacizumab or placebo in patients not deemed fit to receive initial Ir/5FU/LV therapy (Kabbinavar 2005). Results indicate that many patients were of good performance status ultimately receiving Ir or Ox as salvage therapy. Median PFS and OS were improved by 3.7 months each by addition of bevacizumab.

The addition of bevacizumab to these chemotherapy regimens does increase the risk of toxicity. The major form this has taken has been in raised blood pressure with 11% of patients within the IFL +/- bevacizumab study showing grade 3 hypertension. Most of this however was well controlled on anti-hypertensive medication. Increased rates of arterial thrombo-embolism (ATE), bleeding, delayed wound healing and perforation of the gastro-intestinal (GI) tract have been observed in the published trials. A study of bevacizumab used in almost 2000 patients treated in a community setting (Kozloff 2006) has given further information regarding these toxicities. The incidence of GI perforation was 1.7%; ATE – 2.1% and significant bleeding 1.9% with 12% of patients experiencing a serious adverse event. A prior history of peptic ulcer disease or diverticulosis or use of anti-inflammatory medication including aspirin did not seem to increase the likelihood of GI perforation. The presence of the primary colonic tumour remaining *in-situ* appears to double the risk of GI perforation or bleeding although the absolute risk remains small (3.6% and 7.2% respectively) (Kretzschmer 2006). It also appears that most perforations will occur within the first 3 months.

Patients in the community based study appear more representative of the general aCRC population and it is of interest that median PFS of this group of patients to date is 11.3 months. The results of using bevacizumab as salvage therapy after failure of conventional chemotherapy regimens appears disappointing to date (Chen 2004)

Cetuximab – clinical data and experience

The epidermal growth factor receptor (EGFr) represents another molecular target within colorectal adenocarcinoma cells whose over-expression is associated with increased proliferation, reduced apoptosis and adverse clinical characteristics.

Cetuximab is a chimeric IgG1 monoclonal antibody that binds to EGFr with high affinity preventing ligand binding and subsequent signal transduction. Pre-clinical data has demonstrated the ability of cetuximab to sensitise tumour cells to chemotherapy, even those with pre-existing chemo-resistance. Initial clinical studies have therefore positioned cetuximab as a salvage therapy after failure on irinotecan and oxaliplatin containing regimens.

A number of trials of cetuximab used in this role have been published to date, all but one non-randomised. Patients have been selected for tumour EGFr expression (immunohistochemical analysis) and in general have been very fit (ECOG 0 –1 or

Karnofsky > 80) for a cohort with advanced disease having failed at least 2 prior chemotherapy regimens. When used as monotherapy cetuximab appears to have an objective response rate of around 10% [Lenz 2005; Cunnigham 2004]. In combination with irinotecan (after failure on, or within 3 months of completion, of an irinotecan containing regimen) response rates in the order of 20 – 25% have been observed with median time to progression of 4 – 5 months (Cunningham 2004). About 25% of patients have survived more than 1 year.

In general the toxicity from cetuximab has been well tolerated. Diarrhoea, neutropenia and fatigue are observed when cetuximab is combined with irinotecan although at frequencies that would be observed with irinotecan alone. However, in a small study of cetuximab in combination with irinotecan/5FU/LV as first line therapy there was a suggestion of increased toxicity when compared to the non-cetuximab containing regimen in previous studies. The most frequent toxicity observed is dermatological with acneiform skin rash being predominant but seborrheic dermatitis and paronychia also causing problems. The acneiform rash tends to occur within 30 days of starting therapy (although may take over twice this length to appear). At its worst this rash can be disfiguring and painful although it appears to respond well to oral antibiotics particularly if commenced at the first signs of the rash.

The main interest in the cutaneous toxicity arising from cetuximab is that it may represent a surrogate marker of benefit in terms of response and survival. There is mounting data to suggest that tumour staining for EGFR is not a reliable predictor for benefit from cetuximab. A number of studies have shown that patients developing grade 2 or 3 skin rash whilst on cetuximab have significantly better responses and survival compared to those with mild or no skin rash (Cunningham 2004). However, this hypothesis requires further supporting evidence before being used to guide patient treatment.

Studies are ongoing using cetuximab in combination with irinotecan and oxaliplatin containing regimens as first line therapy for advanced CRC. Although early data shows evidence of high response rates results remain immature at present.

Perspective

The introduction of novel targeted therapies into the treatment of cancer has been heralded as the dawning of a new age of more effective cancer management.

However, in aCRC this understandable optimism has to be tempered by a number of important points.

1. The paucity of randomised trial data published in peer reviewed journals, although this is likely to change substantially over the next few years.
2. Trial patients not properly representing the general population with aCRC (tending to be younger and fitter as is common in clinical trials).
3. The increasing cost of treating aCRC with the introduction of each wave of new agents. This is increasingly taxing the minds not only of policy makers and doctors in state funded health care systems but also in those with personal insurance based provision.

Undoubtedly with further research and increased experience these issues may change. Thus particular patient groups may be identified who are more likely to respond to bevacizumab and cetuximab; the optimal duration of treatment may be clarified etc.

In summary;

Bevacizumab:

1. 1st line in combination with 5FU/LV/Ir – statistically and clinically significant improvements in response and overall survival
   Supported by data from one good pivotal randomised trial
   Data collected and presented on use in community setting
   Scientific rationale that combination with more effective 5FU/LV/Ir regimens should continue to bring benefit.
2. Toxicity manageable in general, although small number of patients may experience serious or life threatening side effects. High risk patients and / or situations (e.g. surgery) may be predictable.
3. Rationale for selecting patients for treatment to mimic the original trial population e.g. comparatively young, good performance status and adequately preserved organ function.

Cetuximab

1. Addition to Irinotecan in 2nd or 3rd line therapy results in statistically significant but clinically modest improvements in survival.
   As yet supported by less robust clinical data
   Tumour EGFR staining by immunohistochemistry as predictor of response – little supporting data

Intensity of skin rash as predictor of response – increasing supporting data.

2. Additional toxicity modest

References

Chen, HX., et al
Bevacizumab plus 5FU/Leucovorin for advanced colorectal cancer that progressed after standard chemotherapies: an NCI treatment referral centre trial (TRC-0301)
ASCO annual meeting. 2004. abstract #3515

Cunningham D et al
Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer
New England Journal of Medicine. 2004; 351(4):337-45

Grothey A et al
Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment.
Journal of Clinical Oncology. 2004; 22(7): 1209-14

Hurwitz, H. et al
Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.
New England Journal of Medicine. 2004; 350(23):2335-42

Kabbinavar, FF. et al
Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer :results of a randomised phase II trial
Journal of Clinical Oncology. 2005; 23(16): 3697-705

Kozloff, M. et al
Safety of bevacizumab (bv) among patients (pts) receiving first-line chemotherapy for metastatic colorectal cancer: updated results from a large observational study in the USA (BRITE)
ASCO gastrointestinal cancers symposium. 2006. Abstract #247

Kretzschmer, A. Et al
Incidence of gastrointestinal perforation and bleeding in patients starting bevacizumab in first-line treatment of metastatic colorectal cancer without primary tumour resection. Preliminary results from the first BEAT study.
ASCO gastrointestinal cancers symposium. 2006. Abstract #248

Lenz, HJ. et al
Consistent response to treatment with cetuximab monotherapy in patients with metastatic colorectal cancer.
ASCO annual meeting. 2005. Abstract #3536

Nygren, P et al
Targeted drugs in metastatic colorectal cancer with special emphasis on guidelines for the use of bevacizumab and cetuximab; an Acta Oncologica expert report.
Acta Oncologica 2005; 44: 203-217

Seymour, MT. et al
Fluorouracil, Oxaliplatin and CPT-11 (Irinotecan); Use and sequencing (MRC FOCUS); a 2135-patient randomised trial in advanced colorectal cancer (ACRC)
ASCO annual meeting 2005. Abstract #3518

Tournigand, C. et al
FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomised GERCOR study.
Journal of Clinical Oncology. 2004; 22(2): 229-37