The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

Introduction

In the past systemic cancer treatment has centered on the use of drugs, largely discovered serendipitously, which are essentially indiscriminant DNA poisons. However with increasing knowledge of cell biology at the molecular level including the mechanisms of carcinogenesis it is now possible to develop drugs directed at specific targets with the promise of more effective and less toxic therapies. Monoclonal antibodies represent one such approach and several including rituximab and herceptin have entered routine clinical practice. There are now two monoclonal antibodies which have shown considerable promise in the treatment of advanced colorectal cancer bevacizumab and cetuximab.

Bevacizumab

Bevacizumab is a recombinant humanised monoclonal antibody that targets vascular endothelial growth factor (VEGF) and is thought to inhibit new blood vessel formation by binding to VEGF. All cancers need a blood supply in order to continue to survive, grow and metastasise and thus prevention of new vessel formation should have a central effect in limiting tumour progression. In addition this restriction of new vessel formation appears to reduce the interstitial pressure within the tumour thus allowing improved access for chemotherapy drugs and an enhanced therapeutic effect.

A large phase III randomised trial (Hurwitz et al) comparing chemotherapy (IFL - Irinotecan + 5FU + folinic acid) + / - bevacizumab in patients with advanced colorectal cancer has shown increased response rates and significant improvements in survival for the patients receiving bevacizumab (Hurwitz et al.). The overall response rates were 45% vs 35% ($p=0.004$) and duration of response 10.4 vs 7.1 months $p=0.0014$. Overall median survival was 20.3m in the IFL-bev arm compared to 15.6m in the IFL alone arm $p<0.001$. Two earlier randomised phase II trials comparing 5FU + folinic acid +/- bevacizumab also suggested benefits for the patients receiving bevacizumab in terms of response rate and median survival.

Bevacizumab has also been shown to enhance the effect of oxaliplatin based chemotherapy both as first line treatment (TREE-2 trial) and as second line treatment following previous Irinotecan + fluoropyrimidine (ECOG E3200). However these data are preliminary and the advantage in second line therapy rather small.

There are limited data on the optimum duration of bevacizumab therapy. In the Hurwitz trial patients were able to continue bevacizumab for up to 96 weeks or until progression of their disease and a number of patients had to discontinue IFL due to toxicity but continued with bevacizumab. However the single agent response rate to bevacizumab is low and it is unknown if continuing the drug in this manner is beneficial. At present there are no data to support the use of bevacizumab as part of second line treatment following failure of a bevacizumab containing first line regimen but a trial addressing this question is ongoing.

Bevacizumab treatment carries an increased risk of thromboembolic events, hypertension and impaired wound healing. The drug should therefore be avoided in patients with a history of arterial thrombotic events, uncontrolled hypertension, serious non-healing wounds and within 28 days of surgery.

There is therefore evidence to support the use of bevacizumab in combination with chemotherapy as first line treatment for advanced colorectal cancer. However the median survival from the Hurwitz trials for the patients receiving chemotherapy (IFL) + bevacizumab was 20.3 months and this is similar to the 21 months median survival from the FOLFIRI/FOLFOX crossover trial, undertaken in the pre-bevacizumab era. A relatively small subgroup of the patients in the Hurwitz study went on to second line oxaliplatin based chemotherapy on progression and for this group the median survival was 25 months. It is likely therefore that the addition of bevacizumab to a FOLFIRI/FOLFOX crossover strategy would result in an improved median survival of 3-4 months but these data are not yet available. The optimum duration of bevacizumab therapy is also not clear and it is unknown whether or not continuing the drug with second line chemotherapy is of value.

Cetuximab

Abnormalities in the regulation and expression of growth factors and/or their receptors play a key role in the development and subsequent growth and spread of malignancies. The epidermal growth factor receptor is over expressed in a number of human tumours including colorectal cancer and activation of the receptor has profound effects on cellular growth, differentiation and proliferation.

Cetuximab is a chimeric human-mouse monoclonal antibody directed against the ligand-binding site of the EGFr and initial preclinical studies showed that cetuximab could inhibit the growth of tumour cells overexpressing EGFr. Futher studies suggested synergy between cetuximab and irinotecan with the ability of the combination to reverse irinotecan resistance. This led to a series of phase II trials in patients with EGFR irinotecan resistant tumours culminating in a randomised phase II trial (BOND study) which compared cetuximab alone with cetuximab + irinotecan in a group of patients with EGFR +ve irinotecan resistant advanced colorectal cancer. The relative response rates were 10.8% and 22.8% $p<0.001$ and time to progression 1.5 vs 4.1 months $p<0.001$ however there was no difference in median survival 6.9 months vs 8.6 $p=0.48$ possibly due to treatment crossover on progression.

A number of trials have looked at the use of cetuximab in other situations. The most interesting of these is a phase II trial combining FOLFOX with cetuximab which achieved a response rate of 81% with a further 17% disease stabilisation and a progression free survival of 12.3 months. If confirmed response rates of this magnitude could significantly increase the numbers of patients able to go forward for potentially curative liver surgery.

Patients were selected for entry into the earlier clinical trials on the basis of EGFR receptor positivity as determined by immunohistochemistry. However subsequent studies have failed to demonstrate a correlation between intensity of staining for

EGFR receptor and response to cetuximab and patients who have EGFR negative tumours using current methods of assessment are just as likely to respond.

The major toxicities associated with cetuximab are hypersensitivity reactions and an acneiform rash. Hypersensitivity reactions are uncommon but are most likely to occur with the first and second cycles. The rash, when it occurs, develops in the early phases of treatment usually reaching a peak at week 3 - 4 before improving. Active management eg with antibiotics and topical steroids can help to reduce the effects of the rash the development of which appears to correlate with the effectiveness of the therapy.

As with many cancers colorectal cancer patients who have responded to systemic chemotherapy are more likely to respond to subsequent treatment than those who have not. Increasingly we are seeing fit patients who have responded to previous treatment but who have now developed drug resistant disease and for whom there is no remaining active therapeutic option. For this group, which probably represents about 5% of all patients with metastatic colorectal cancer, cetuximab provides a new opportunity for treatment which may, in responding patients, provide additional survival in excess of 12 months. Data from the BOND study suggest that it is patients who have a partial response after six weeks therapy who are most likely to benefit thus an evaluation at this time point would serve to allow the early discontinuation of treatment in patients unlikely to be helped.

Conclusions

Bevacizumab and cetuximab provide the promise of exciting advances for the treatment of colorectal cancer however data which inform the most effective way to integrate them into treatment strategies are still emerging. In the future it is likely that the best results in advanced disease will be obtained by the concurrent or sequential use of all five active agents. In addition it is possible that the high response rates resulting from the combined use of chemotherapy + bevacizumab/cetuximab will allow more patients to go forward for potentially curative liver surgery.

For the present it is clear that cetuximab may be of significant benefit to the small group of patients who remain very well but who have developed progressive drug resistant disease following treatment with irinotecan a fluoropyrimidine and oxaliplatin. Cetuximab should be available for these patients. It is less easy to define a specific group of patients who will benefit from bevacizumab. It has little single agent activity and current data have not demonstrated a major improvement in survival that cannot be achieved with conventional chemotherapy.