Treatment of metastatic CRC takes two steps forward

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The US approval of cetuximab and bevacizumab for patients with metastatic colorectal cancer is seen as the dawn of a new era in targeted therapies. Used together with cytotoxic regimens, they can add months to a patient's life – but they don't come cheap.

In early 2004, the FDA (the US drugs regulator) approved two monoclonal antibodies, cetuximab (Erbitux) and bevacizumab (Avastin), for patients with metastatic colorectal cancer (CRC). Trials show that the two drugs, used in conjunction with cytotoxic regimens, produce encouraging extensions of median survival, stabilise tumours and provide welcome further therapeutic options in a group of patients where treatments have been limited.

Statistics show that CRC – which includes cancer of the colon, rectum, anus and appendix – is now the most common site of human non-skin cancers in Europe. In 2000, 304,687 new cases of CRC were diagnosed in Europe, compared to 301,090 cases of lung cancer. In the same year there were 167,184 deaths from CRC in Europe.

Age-specific incidence and mortality rates show that most cases of CRC are diagnosed after 50 years of age. Genetic, experimental, and epidemiological studies suggest that colorectal cancer results from complex interactions between inherited susceptibility, environmental causes and lifestyle factors. Groups with a high incidence of CRC include those with hereditary conditions, such as familial adenomatous polyposis and hereditary non-polyposis colorectal cancer, which together account for around 6% of cases.

Metastatic disease is widespread, with around 30% of CRC patients presenting with advanced disease. One of the main reasons for late diagnosis is that people hide symptoms. A recent survey of 21,000 Europeans by the United European Gastric Federation revealed that 66% of all respondents regarded embarrassment as a barrier to seeking early diagnosis for CRC. Overall, the five-year case-fatality rate is 50%, but for localised disease the five-year survival rate approaches 90% for cancer of the colon and 80% for cancer of the rectum.

In patients with metastatic CRC, chemotherapy has been effective in prolonging survival and time to disease progression. Without chemotherapy, the median duration of survival among patients with metastatic CRC was eight months. With the introduction of fluorouracil, it increased to 12 months. Then, over the last five years, availability of other cytotoxic agents (capecitabine, irinotecan and oxaliplatin) further extended median survival to 21 months. But once these three standard drugs had failed, there were no further treatment options. Now it is anticipated that the use of cetuximab and bevacizumab will have an additional impact on survival.

Cetuximab

On 12 February 2004, the FDA approved cetuximab under its accelerated approval programme as an intravenous combination treatment with irinotecan for the treatment of patients with metastatic CRC, or for use alone if patients cannot tolerate irinotecan. Approval in Europe followed in June.

Cetuximab, is a monoclonal antibody against the epidermal growth factor receptor (EGFR) which, when activated, contributes to cellular proliferation, migration, angiogenesis and apoptosis, all of which become deregulated in cancer cells. EGFR is of particular relevance in CRC, since expression or up-regulation of the EGF-receptor occurs in 60–80% of cases. In addition, expression of the

receptor is known to be associated with poor survival.

Approval of cetuximab was largely based on the findings of the bowel oncology with cetuximab antibody (BOND) study, published recently in the *New England Journal of Medicine* (vol. 351, pp 337–345). In the study, 329 patients with EGFR-expressing metastatic CRC, whose disease had progressed after receiving irinotecan, were randomised in a 2:1 fashion to receive the combination of cetuximab and irinotecan or cetuximab monotherapy.

Results showed the response rate for the 218 patients receiving combination therapy was 22.9%, compared to 10.8% for the 111 patients receiving monotherapy (p=0.007). The median time to progression was 4.1 months for the combination therapy group compared to 1.5 months for the monotherapy group (p<0.001), and median survival was 8.6 months for the combination therapy group, compared to 6.9 months in the monotherapy group (p=0.48). "The combination therapy group had a significantly higher response rate and a significantly longer time to progression than the monotherapy group, suggesting that the combination of irinotecan and cetuximab should be preferred for patients with irinotecan refractory cancer," write the authors.

The effectiveness of combination therapy suggests that cetuximab may work by circumventing irinotecan resistance. The authors hypothesise that EGFR inhibition by cetuximab may overcome resistance by abrogating drug efflux, restoring apoptosis or impairing DNA-repair activity.

Eric van Cutsem: concerns over drug costs must not get in the way of significant advances in biomedical research

Roberto Labianca: approval of bevacizumab is significant as this is the first angiogenesis inhibitor shown to be efficacious in human cancer

"There was a wide variety of response. In some patients we could control the cancer for one or two years, while in others we couldn't achieve anything," said Eric Van Cutsem, one of the lead researchers in the study, and chairman of the EORTC Gastrointestinal Tract Cancer Group.

The study was not, he added, designed to show an effect on overall survival. This will be explored in the new trials currently underway in patients with metastatic disease who have not received previous treatment. Here, patients are being randomised to receive standard chemotherapy or standard chemotherapy plus cetuximab – a design considered comparable to the bevacizumab study (see below).

Bevacizumab

On 26 February 2004 the FDA approved bevacizumab as a first-line treatment for patients with metastatic CRC. The drug was approved for use in combination with intravenous 5-fluorouracil-based chemotherapy for treatment of people diagnosed with metastatic CRC for the first time.

"The approval of bevacizumab is of particular note since it's the first time that an angiogenesis inhibitor has been shown to be efficacious in human cancer," said Roberto Labianca, director of the Oncology Department of Ospedalia Riuniti and president of AIOM, the Italian medical oncology society. At the end of October, bevacizumab was given a positive opinion by the Committee for Human Medicinal Products (CHMP), and it is now awaiting full approval by the EC.

"With an average survival gain of five months, a fraction of patients will live a lot longer"

"The implications of these two studies are great for the management of advanced CRC"

In their phase III trial assessing bevacizumab (*N Engl J Med* 2004; 350:2335–2342), Herbert Hurwitz and colleagues, from Duke University Medical Center, Durham, US, randomly assigned 813 patients with previously untreated metastatic colorectal cancer to one of two groups. The first group received IFL (the addition of irinotecan to the fluorouracil and leucovorin systemic treatment, also known as the Saltz regimen) plus bevacizumab, while the second received IFL plus placebo.

Results showed that the median overall survival for patients who received IFL plus bevacizumab was 20.3 months compared to a median overall survival of 15.6 months for those who received just IFL ($p<0.001$). "The increase of 4.7 months in the median duration of survival attributable to bevacizumab is as large or larger than that observed in any other phase III trial for the treatment of colorectal cancer," wrote the authors. In addition, the median progression-free survival increased from 6.2 months to 10.6 months ($p<0.001$) for patients given bevacizumab, and the objective response rate was 44.8% versus 34.8% ($p=0.004$).

Labianca commented: "I think that the gain of five months in overall survival obtained by bevacizumab is important, because it means that a fraction of the patients will achieve much longer survival or might even be cured. It suggests that in the adjuvant setting we have the potential to cure many patients." Van Cutsem added that another way of presenting these results, which might have demonstrated greater advantage for the bevacizumab combined treatment, would be to look at the number of patients alive at two years and compare this to controls.

Two steps forward

Commenting on both sets of findings, Van Cutsem said: "Taken together, the implications of these two studies are great for the management of advanced colorectal cancer. Here are two drugs that are well tolerated, that can either prolong life or stabilise tumours so that patients achieve a better quality of life."

He adds that criticisms levelled at the targeted therapies that they do not affect cure rates are premature, since, to show an effect on cure rates, trials are needed in the adjuvant setting. "For both cetuximab and bevacizumab trials are now planned where patients will undergo surgical resection and then be randomised to receive standard chemotherapy or chemotherapy plus the addition of cetuximab or bevacizumab (adjuvant setting). This will show whether the agents can decrease the chance of recurrence," said Van Cutsem. But the financial costs of these new treatments is an issue. In an accompanying editorial to the cetuximab study (*N Engl J Med* 2004; 351:317–319), Deborah Schrag, from the Memorial Sloan-Kettering Cancer Center, New York, estimates that the addition of monoclonal-antibody therapy to the eight-week course of initial treatment for the 56,000 patients in the US

David Cunningham: challenge for the future is to define the populations who are most likely to benefit from the new therapies

Mike Keighley: introduction of widespread screening programmes would deliver a far greater impact on overall survival

who receive a diagnosis of stage IV CRC and recurrent metastatic disease each year, would cost $1.2 billion (961,000 euros). She adds that these costs are exclusively for drugs and do not include the costs of preparation, administration and supervision or supportive medications.

Robert J Mayer, from the Dana-Farber Cancer Institute, Boston, estimated in an accompanying editorial to the bevacizumab study (*N Engl J Med* 2004; 350:2406–2408), that treating a patient who weighed 80 kg with the dose used in the paper for a median of 40.4 weeks would add between $42,800 and $55,000 (34,300–44,100 euros) to the cost of their care. "Unfortunately," writes Schrag "such costly treatment will not provide a cure; one can only speculate about the relative effect of directing these resources towards screening and prevention."

Mike Keighley, chairman of the Public Affairs Committee of the United European Gastroenterology Federation (UEGF), argues that the introduction of widespread screening programmes would deliver a far greater impact on overall survival from CRC than treating end-stage disease. He quoted results from a recent 18-year Danish Screening Programme by Professor Ole Kronborg, from Odense University Hospital, suggesting screening with a faecal occult blood test (FOBT) reduced CRC deaths by 43% for individuals who had participated in the full 18-year programme.

Still no screening?

"Estimates suggest that if we could get FOBT uptake rates of 70% we could halve the death rate of CRC, while the evidence that the new drugs are hugely superior is lacking," said Keighley. "It could be argued that treating metastatic disease is shutting the door after the horse has bolted.

"But screening is up against the problem that public health experts have a low presence compared to powerful patient lobbies."

It is a question of priorities, and Keighley believes governments have got them wrong. He points out that although screening for CRC became EU policy in November 2003, not a single European country has yet introduced a comprehensive screening programme.

David Cunningham, a lead author on the cetuximab paper, from the Royal Marsden Hospital, London, agreed that ongoing efforts in the area of screening are crucial, but stressed that they should not be counterposed to attempts to improve outcomes for patients who present with advanced disease, and efforts in the two areas need to occur in parallel.

The challenge for the future, both maintain, is to define the populations who are most likely to benefit from new therapies. "This would ensure both appropriate use of resources and minimisation of adverse effects," said Cunningham. Studies with cetuximab show a correlation between the development of a maculopapular rash (a characteristic side-effect of EGFR blockade) and the likelihood of a positive response, which Cunningham believes could potentially be used to determine which patients may benefit from therapy. However, he stressed the need to await the results of prospective evaluation study that is currently in progress, and added that "emerging data and data from the studies suggest that the level of EGFR expression does not correlate with response, and EGFR expression alone may therefore not be the most appropriate method to select patients for therapy."

Van Cutsem said that his group was undertaking tumour biopsies of patients treated with cetuximab, to see whether the presence of different enzymes, such as MAP kinase and AKT, might predict outcome.

Labianca believes that in the mean time clear guidance is needed for oncologists faced with making costly decisions. "The scientific societies, such as ESMO in Europe and AIOM in Italy, need to give clinicians a steer with the establishment of guidelines for the treatment of CRC that can be updated according to each advance," he said.

On the basis of the trials, he added, there are now two settings where the new agents might be offered. He felt it reasonable that cetuximab might be offered second or third line after irinotecan escape, and that bevacizumab, combined with irinotecan-based chemotherapy, might provide first-line treatment for patients in whom it was hoped to produce curative effects.

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