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Cetuximab

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Cetuximab (C225, Erbitux™) is a chimeric monoclonal antibody (MAb) targeting the epidermal growth factor receptor (EGFR), a transmembrane structure with tyrosine kinase activity which is overexpressed in up to 80% of colorectal cancers. The ligand EGF is relevant for tumour cell proliferation, apoptosis, angiogenesis, invasion and metastasis. The binding of cetuximab induces inhibition and downregulation of the EGFR and a broad range of cellular responses (inhibition of cell cycle progression, induction of programmed cell death and a decrease in production of autocrine growth factors). In preclinical models, the MAb enhances the activity of various anticancer agents and even reverses resistance to agents such as irinotecan, acts as a radiosensitiser, decreases angiogenesis and inhibits cancer cell invasion. In cancer patients, the MAb is commonly given as a 1–2 hour intravenous infusion at a weekly maintenance dose of 250 mg/m^2 after initial loading. Common clinical toxicities are rash, fatigue, abdominal pain, nausea/vomiting and hypersensitivity.

In colorectal cancer trials, cetuximab has mainly been used in EGFR-positive tumours failing irinotecan-based treatment, and smaller trials have explored its use in treatment-naive patients. At present, most clinical results are available in abstract form only. The single agent activity in colorectal cancer refractory to both irinotecan and fluorouracil is 11% (6/57 patients). In 19% of 121 patients progressing on irinotecan, the addition of cetuximab to the same regimen did overcome resistance to the topoisomerase-1 inhibitor and achieved a partial response. In a similar cohort with irinotecan-refractory colorectal cancer, the combination of irinotecan with the MAb induced significantly higher partial response rates than cetuximab alone (22.9% vs 10.8%; $p = 0.0074$) and extended the time to disease progression (4.1 vs 1.5 months; $p < 0.0001$). In treatment-naive patients, cetuximab was safely combined with irinotecan and fluorouracil in three smaller, independent trials and achieved preliminary partial response rates of 43–58%. Cetuximab was approved for treatment of colorectal cancer in Switzerland in December 2003.

To conclude, cetuximab is a well tolerated, active agent for treatment of advanced colorectal cancer, requiring further trials both in treatment-naive and pretreated patients. Additional studies are warranted in combination with radiotherapy for rectal cancer and in the adjuvant setting of colon cancer, respectively. Among the multitude of innovative targeted agents for treatment of human cancers, the monoclonal EGFR inhibitor appears to be a very promising candidate for this common tumour type. ▲