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Cetuximab

In the Treatment of Metastatic Colorectal Cancer

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Contents

Abstract

▲ Cetuximab is a chimeric monoclonal antibody highly selective for the epidermal growth factor receptor (EGFR), which is over-expressed by 25–80% of colorectal cancer tumours and associated with advanced disease.

▲ Cetuximab induces a broad range of cellular responses in tumours expressing EGFR, enhancing sensitivity to radiotherapy and chemotherapeutic agents.

▲ In a large, randomised, open-label, multicentre study in adult patients with irinotecan-refractory, metastatic colorectal cancer expressing EGFR, cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly plus irinotecan (various doses) produced a greater rate of partial response and disease control (partial response plus stable disease), and increased time to disease progression, compared with cetuximab monotherapy; survival was similar in both groups.

▲ The same dosage of cetuximab combined with irinotecan, fluorouracil and folinic acid (various regimens) produced partial responses in 43–58% of patients, a complete response in 5% of patients (one study only) and stable disease in 32–52% of patients with treatment-naive metastatic colorectal cancer expressing EGFR in three small, open-label trials.

▲ The most common grade 3/4 adverse events associated with cetuximab monotherapy were acne-like rash, asthenia, abdominal pain and nausea/vomiting. In patients receiving cetuximab plus irinotecan, these were diarrhoea, asthenia, leucopenia and neutropenia.

Features and properties of cetuximab (IMC-C225, Erbitux™)	
Indication	
Treatment of metastatic colorectal cancer expressing epidermal growth factor receptor (EGFR) in combination with irinotecan-based chemotherapy regimens	
Mechanism of action	
Chimeric monoclonal antibody selective for the EGFR that induces a broad range of cellular responses that enhance tumour sensitivity to radiotherapy and chemotherapeutic agents	
Dosage and administration (in clinical trials)	
Dosage	400 mg/m^2 initial dose followed by 250 mg/m^2 weekly
Method of administration	Intravenous infusion; initial dose (120 min), weekly dose (60 min)
Pharmacokinetic profile (400 mg/m^2 initial dose followed by 250 mg/m^2 weekly)	
Mean peak serum concentration	153–202 μg/mL
Mean volume of distribution	45.2–61.9 mL/kg
Metabolism	Removed from circulation through internalisation of the cetuximab-EGFR complex on hepatocytes and skin; saturable metabolism
Mean elimination half-life	79–129 hours
Adverse events	
Most frequent	Acne-like rash, asthenia, abdominal pain, nausea/vomiting

According to the American Cancer Society estimates for 2003, colorectal cancer accounts for 11% of cases of cancer in the US, and is responsible for 10% and 11% of cancer-related deaths in men and women, respectively.[1] The initial treatment of colorectal cancer is surgical,[2-4] but the disease recurs in 40–60% of patients,[2,4-6] generally at distant sites, such as the liver, lungs, bone and pelvis,[5] due to the presence of micrometastases at the time of surgery. The prognosis for patients who develop advanced, metastatic disease is poor, with a median survival with modern three-drug combinations from time of diagnosis of 14–18 months.[7]

Chemotherapy is indicated for patients with advanced disease;[2-5,8] the therapeutic aim is to prolong survival, control symptoms and maintain or improve quality of life.[2] Fluorouracil, administered systemically with or without folinic acid, has formed the basis of first-line treatment regimens for several decades and has been shown to prolong symptom-free and overall patient survival[3-5,8] and improve quality of life.[5] However, more recently, new chemotherapeutic agents have become available that have increased response rates, time to disease progression and survival in patients with metastatic colorectal cancer, such as irinotecan[9,10] and oxaliplatin.[11,12] In practice, these drugs are used as first- and second-line therapy;[7] although their use increases efficacy outcome in metastatic colorectal cancer, there is still need for further improvement.

The epidermal growth factor receptor (EGFR) is a transmembrane receptor possessing tyrosine kinase activity which is stimulated by growth factors such as transforming growth factor-α (TGFα) and EGF.[13-16] This receptor is over-expressed by a variety of tumour cell lines, including 25–80% of colorectal carcinomas,[15,16] and is associated with advanced disease.[16] Furthermore, EGF is crucial for tumour cell proliferation, inhibition of apoptosis and other processes important for cancer progression, including angiogenesis, invasion and metastasis,[13-16] making EGF a promising target for anticancer agents.[13-17]

Cetuximab (Erbitux™[1]) is a chimeric monoclonal antibody that binds selectively to the EGFR and has shown antitumour activity against a variety of cancer cell lines in preclinical studies.[13,14,16] Cetuximab has demonstrated efficacy in head and neck and non–small-cell lung cancer;[13,14,16] however, this profile focuses on the role of cetuximab in the treatment of patients with metastatic colorectal cancer, administered alone or in combination with irinotecan-based chemotherapy regimens.

1. Pharmacodynamic Profile

The pharmacodynamic properties of cetuximab, also named IMC-C225 or C225, have been reviewed in detail by Baselga[13] and Kim et al.,[14] and are briefly described below.

Mechanisms of Action

- Cetuximab has a higher affinity for the EGFR than either EGF or TGFα and competitively blocks the cellular action of these naturally occurring ligands.[13,14] Cetuximab is also understood to promote receptor internalisation, thereby down-regulating the EGFR.[18]
- The antitumour activity of cetuximab is thought to occur through several mechanisms.[13] Cetuximab inhibits cell cycle progression in the G_1 gap phase that occurs prior to DNA synthesis, through increased expression of the cell cycle inhibitor $p27^{kip1}$[19] and a reduction of proliferating cell nuclear antigen expression.[13] Cetuximab also induces cancer cell apoptosis, by altering the ratio of Bax to Bcl-2 expression,[19] and by increasing expression of apoptotic caspases.[13,14]
- Cetuximab decreases the production of autocrine growth factors, including TGFα,[20,21] amphiregulin[20] and cripto,[20] and angiogenic factors associated with the proliferation of microvessels, including vascular endothelial growth factor (VEGF),[20-22] basic fibroblast growth factor[20-22] and interleukin-8.[22] There is also evidence that cetuximab therapy inhibits tumour-cell invasion and metastasis, possibly by inhibiting the expression and activity of

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

molecules that play a key role in tumour-cell adhesion, such as matrix metalloproteinase-9.[23]

Antitumour Effects

With Topoisomerase I Inhibitors

- Cetuximab enhanced the antitumour effects of several chemotherapeutic agents in athymic mice xenograft models of human colon cancer (cell lines DLD-1 and HT-29).[24,25] Cetuximab used in combination with irinotecan significantly improved inhibition of tumour growth in both cell lines compared with the individual agents used alone ($p < 0.05$).[24] Tumour regression was not reported for the agents used separately.[24] Further, in an irinotecan-refractory tumour model (cell lines DLD-1 and HT-29) combination therapy with cetuximab plus irinotecan significantly ($p < 0.01$) inhibited tumour growth whereas the individual agents used alone did not.[24]
- In athymic mice xenograft models of human colon cancer (using cell lines DLD-1 and HT-29), cetuximab inhibited tumour growth by 48% and 29%, for the respective cell lines.[25] The combination of irinotecan, fluorouracil and folinic acid significantly inhibited growth in both cell lines (values not stated) and resulted in regression of tumours in 25% of mice.[25] The addition of cetuximab to this combination inhibited tumour growth by 76% and 80%, and resulted in tumour regression in 38% and 45% of mice with DLD-1 and HT-29 tumours, respectively.[25] This combination left 16% of mice tumour-free 3 weeks after treatment cessation.[25]
- Cetuximab enhanced the antitumour effects of topotecan on human GEO colon cancer cells *in vitro*.[26] Cells treated with topotecan or cetuximab alone demonstrated ≈10% tumour growth inhibition, whereas treatment with the two agents caused a 50% inhibition in tumour growth.[26] Furthermore, apoptosis was observed in 45% of cells treated with both agents compared with 22% of cells treated with topotecan alone.[26] Cetuximab alone did not induce apoptosis in this cell line.[26]
- Cetuximab has also shown a complementary interaction with topotecan in a murine xenograft model of human GEO colon cancer cells *in vivo*.[26] Treatment with either drug alone produced temporary inhibition of tumour growth, which resumed at the previous rate on treatment cessation.[26] However, almost complete tumour regression and a significantly ($p < 0.001$) prolonged life-span compared with monotherapy was seen using sequential treatment with the two agents.[26]

Other Combinations

- Cetuximab also has additive effects with molecules that inhibit the effects of VEGF[21,27] and protein kinase A type I (PKAI)[20,28] in human colon cancer xenografts. Combination therapy of these agents with cetuximab increased tumour growth suppression[20,21,27,28] and apoptosis,[27] reduced tumour angiogenesis[20,21,27] and prolonged mouse survival,[20,21,28] suggesting future therapeutic options.

With Radiotherapy

- Cetuximab enhances radiosensitivity and amplifies radiation-induced apoptosis in carcinoma cell lines.[19,28,29] An additive antitumour effect was seen *in vitro* when human GEO colon cancer cells were treated with ionising radiation in combination with cetuximab and/or a PKAI inhibitor, potentiating the dose-dependent inhibition of tumour growth seen when the three agents were used alone.[28]
- A complementary interaction between cetuximab and radiotherapy has also been demonstrated *in vivo* in a murine xenograft model of human GEO colon cancer cells.[29] Monotherapy with either agent temporarily inhibited tumour growth in a dose-dependent manner, while combination treatment produced a greater and longer lasting inhibition of tumour growth, and resulted in significantly improved survival compared with the monotherapy (p value not stated).[29]

2. Pharmacokinetic Profile

Absorption and Distribution

- In two multiple-dose studies in 13 and 19 patients with metastatic colorectal cancer, mean peak serum concentrations of 153–202 μg/mL and area under the plasma concentration-time curve values of 12 520–17 337 μg • h/mL were recorded between

weeks 1 and 4 of treatment.[30,31] Patients received intravenous cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly, administered in conjunction with irinotecan either alone or with folinic acid and fluorouracil in two dosage regimens.[30,31]

- Cetuximab has a mean volume of distribution of 45.2–61.9 mL/kg, approximately equivalent to plasma volume, at intravenous doses of 20–100 mg/m^2 given singly or at weekly intervals for 4–12 weeks, as demonstrated in two phase I, dose-escalation studies in 23 patients with advanced EGFR-overexpressing epithelial tumours.[32]

Metabolism and Excretion

- It has been hypothesised that the major route of cetuximab clearance is through binding of the antibody to EGFR in many tissues, including the liver and the skin, which subsequently internalises the antibody-receptor complex and removes it from circulation.[32,33]
- Cetuximab clearance decreases with increasing dose, suggesting saturation of the metabolic pathway and nonlinear pharmacokinetics at lower doses.[32,34-36] In a phase I, dose-escalation study in patients receiving single or multiple doses of cetuximab either alone or in combination with cisplatin, clearance at doses of 20, 50, 100, 200 and 400 mg/m^2 was 3.09, 1.16, 0.811–0.837, 0.433 and 0.374 mL/h/kg, respectively.[32] The small difference in clearance observed between doses of 200 and 400 mg/m^2 indicates that clearance is dose-independent between these doses.[32]
- Cetuximab has a mean serum elimination half-life of 79–129 hours at a dosage of 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly, after 1–4 weeks of treatment.[30,31] The serum concentration at which elimination is half of its maximum is 410–482 nmol/L (62.3–73.3 μg/mL).[33,36]
- It is recognised that the efficacy of cetuximab is at its maximum when serum levels completely saturate the EGFR.[32,37] Several studies have suggested that continuous saturation of cetuximab clearance and therefore the EGFR is achieved and maintained in the majority of patients with an initial dose of 400–500 mg/m^2, followed by 200–300 mg/m^2 administered weekly.[32,34-36]

Potential Drug Interactions

- Cetuximab does not appear to exhibit pharmacokinetic interaction with either cisplatin,[32] docetaxel,[38] fluorouracil[31] or irinotecan.[30]

3. Therapeutic Efficacy

The efficacy of cetuximab in the treatment of adult patients with metastatic colorectal cancer with tumours positive for EGFR has been studied in six open-label clinical trials published as abstracts.[39-44] Three small trials used cetuximab as first-line therapy in combination with irinotecan and other agents in patients with previously untreated metastatic colorectal cancer[39-41] and three trials were in patients whose disease progressed on irinotecan-based chemotherapy regimens,[42-44] one of which, the Bowel Oncology with Cetuximab Antibody (BOND) study, was a randomised, multicentre study comparing cetuximab monotherapy with cetuximab plus irinotecan.[42]

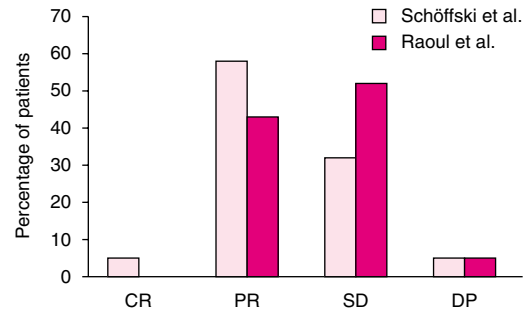

Fig. 1. Cetuximab in treatment-naive patients. Results of two non-comparative trials[39,41] (published as abstracts) in which patients with epidermal growth factor receptor-expressing metastatic colorectal cancer received intravenous cetuximab 400 mg/m^2 followed by 250 mg/m^2 weekly plus intravenous irinotecan-based chemotherapy in the following dosages. Doses were given weekly for 6 weeks in every 7 (n = 19)[41] or every 2 weeks (n = 21)[39]. Patients received irinotecan 80[41] or 180 mg/m^2,[39] folinic acid 500[41] or 400 mg/m^2[39] and low-dose (1500 mg/m^2/24h[41] or 300 mg/m^2 bolus + 2000 mg/m^2/46h[39]) or high-dose (2000 mg/m^2/24h[41] or 400 mg/m^2 bolus + 2400 mg/m^2/46h[39]) fluorouracil. **CR** = complete response; **DP** = disease progression; **PR** = partial response (confirmed + unconfirmed); **SD** = stable disease.

The dosage of cetuximab was the same in all six trials: an initial dose of 400 mg/m^2 followed by a weekly dose of 250 mg/m^2, both administered by intravenous infusion.[39-44] The duration of treatment, stated in one trial only, was one to five 7-week cycles per patient.[41]

The main inclusion criterion for all of the trials was metastatic colorectal cancer with EGFR expression on tumour tissue determined by immunohistochemistry.[39-44]

The primary endpoint, stated only in the BOND study,[42] was objective tumour response rate, evaluated by an independent review committee and reported in accordance with WHO criteria on trial treatment. The WHO defines a complete response as disappearance of all detectable malignant disease for ≥4 weeks, a partial response as a ≥50% decrease in tumour size for ≥4 weeks, stable disease as a <50% decrease and <25% increase in tumour size, and progressive disease as a ≥25% increase in one or more measurable lesions or the appearance of new lesions.[45] Secondary endpoints were time to disease progression[39,42,44] and survival.[42] In several trials, not all patients entered into the trial were suitable for evaluation of endpoint at the time of publication.[39-41,44]

Treatment-Naive Patients

Three trials have reported the use of cetuximab in previously untreated, metastatic colorectal cancer expressing EGFR in combination with irinotecan, folinic acid and fluorouracil, administered intravenously in different regimens.[39-41] Across the three trials, median age was 61–65.4 years[39-41] and disease activity was reflected in a median Karnofsky Performance Status (KPS) of 90–100[39,41] or a median Eastern Cooperative Oncology Group performance status of 1.[40]

Raoul et al.[39] treated 21 evaluable patients with cetuximab plus irinotecan 180 mg/m^2, folinic acid 400 mg/m^2 and fluorouracil in two regimens: low-dose (300 mg/m^2 bolus followed by 2000 mg/m^2 administered over 46 hours) or high-dose (400 mg/m^2 bolus followed by 2400 mg/m^2 administered over 46 hours) every 2 weeks. Rosenberg et al.[40] treated 25 evaluable patients with cetuximab plus weekly irinotecan at a starting dose of 125 mg/m^2, folinic acid 20 mg/m^2 and fluorouracil 500 mg/m^2 for 4 weeks in every 6 weeks. Schöffski et al.[41] treated 19 evaluable patients with cetuximab plus weekly irinotecan 80 mg/m^2, folinic acid 500 mg/m^2 and fluorouracil in two regimens: low-dose (1500 mg/m^2 administered over 24 hours) or high-dose (2000 mg/m^2 administered over 24 hours) for 6 weeks in every 7 weeks.

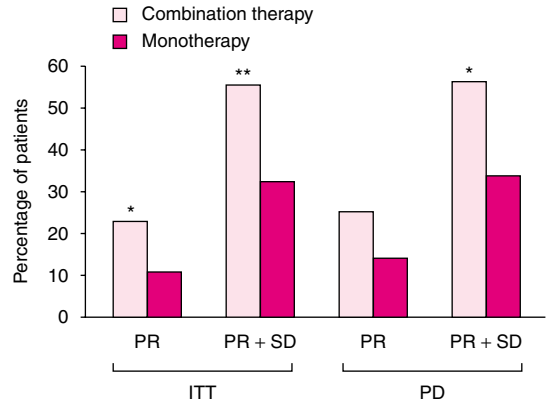

Fig. 2. Cetuximab in irinotecan-refractory patients: response rates in the Bowel Oncology with Cetuximab Antibody study.[42] Patients with metastatic colorectal cancer expressing epidermal growth factor receptor refractory to previous treatment with irinotecan-based chemotherapy regimens received intravenous infusions of cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly alone (n = 111) or in combination with irinotecan (in the same dosage regimen previously resulting in progression; n = 218). Results of this randomised open-label trial[42] are shown for patients whose disease progressed during or ≤12 weeks after treatment (ITT cohort) and those whose disease progressed early (during or ≤30 days after treatment; PD cohort; n = 135 and 71 in the combination and monotherapy groups). **ITT** = intention-to-treat; **PD** = progressive disease; **PR** = partial response; **SD** = stable disease; * $p < 0.01$, ** $p = 0.0001$ vs monotherapy.

- In two of these studies, cetuximab in this combination produced partial responses in 43%[39] and 58% (53% confirmed)[41] of patients, and a complete response occurred in one patient (5%) in one trial[41] (figure 1). Stable disease was observed in 32%[41] and 52%[39] of patients and progressive disease was reported in 5% in both trials[39,41] (figure 1). Median time to disease progression, reported in one trial, was 183 days.[39] The third trial reported a partial

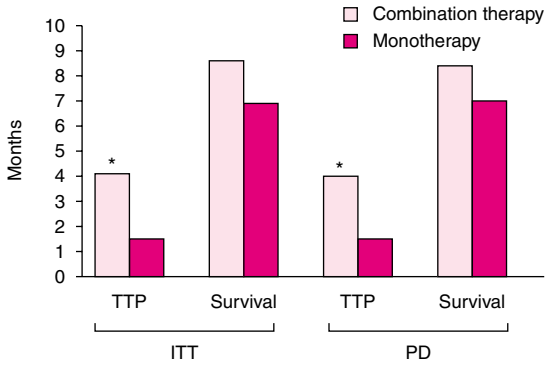

Fig. 3. Cetuximab in irinotecan-refractory patients - progression and survival in the Bowel Oncology with Cetuximab Antibody study.[42] Response to treatment in patients with metastatic colorectal cancer expressing epidermal growth factor receptor refractory to irinotecan-based chemotherapy. Median TTP and survival in patients treated with cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly administered by intravenous infusion alone (n = 111) or in combination with irinotecan (in the same dosage regimen previously resulting in progression; n = 218). Results are from a randomised, multicentre, open-label trial in patients who experienced progressive disease during or ≤12 weeks after previous treatment (ITT cohort) and include a subset of patients with disease progressing during or ≤30 days after previous treatment (PD cohort; n = 135 and 71 in the combination and monotherapy groups).[42] Data available at 16 months. **ITT** = intention-to-treat; **PD** = progressive disease; **TTP** = time to disease progression; * p < 0.0001 vs monotherapy.

response in 44% and a minor response (>40% reduction in tumour size) in 20% of patients.[40]

Irinotecan-Refractory Patients

Inclusion criteria for the BOND study included disease progression during or within 3 months after treatment with a licensed irinotecan regimen, KPS ≥60 and adequate bone marrow, hepatic and renal function.[42] This trial gave most results for the intention-to-treat (ITT) cohort; however, results from a subset of patients who had progressed early on previous therapy (during or within 30 days after treatment; the PD cohort) were analysed separately.[42]

In this large study, patients were randomised to receive cetuximab plus irinotecan (in the same dosage regimen previously resulting in progression [125 mg/m^2 weekly, 180 mg/m^2 every 2 weeks or 350 mg/m^2 every 3 weeks]; n = 218) or cetuximab monotherapy (n = 111).[42] Median patient age was 58–59 years.[42] Patients receiving cetuximab monotherapy had the option of switching to combination therapy with cetuximab plus irinotecan after failure of cetuximab as a single agent.[42]

- In the BOND study, combination therapy with cetuximab and irinotecan produced a significantly greater response rate than cetuximab alone in the ITT cohort (figure 2).[42] Partial response rates were 22.9% in the combination group and 10.8% in the monotherapy group (p = 0.0074).[42] Stable disease rates were 32.6% and 21.6%, respectively.[42] No complete responses were reported in either treatment arm.[42] Disease control (partial response plus stable disease) rates were significantly higher in those receiving combination therapy than in those receiving monotherapy (55.5% vs 32.4%; p = 0.0001) [figure 2].[42]

- Fifty-four patients initially randomised to cetuximab monotherapy in the BOND study were switched to treatment with cetuximab plus irinotecan because of disease progression.[42] In this group, one patient (1.9%) subsequently had a partial response to treatment and 21 patients (38.9%) showed stable disease.[42]

- Combination therapy with cetuximab and irinotecan significantly extended the median time to disease progression compared with cetuximab monotherapy in the BOND study (figure 3).[42] Median times to disease progression in the combination therapy and monotherapy groups were 4.1 and 1.5 months, respectively (p < 0.0001).[42] Median survival durations were 8.6 and 6.9 months.[42]

- In the PD cohort of the BOND study, partial responses (figure 2) and stable disease were seen in 25.2% and 31.1% of recipients of the combination (n = 135), and 14.1% and 19.7% of monotherapy recipients (n = 71).[42] A statistically significant difference between the groups was noted for patients achieving disease control (56.3 vs 33.8%; p = 0.0032; figure 2).[42] At the 16-month follow up, median times to disease progression were 4.0 and 1.5 months in the combination treatment group and monotherapy recipients, respectively (p < 0.0001), and patients had survived for a median of 8.4 and 7.0 months (figure 3).[42]

- The preliminary efficacy of cetuximab monotherapy in 57 patients with EGFR-positive colorectal cancer refractory to both irinotecan and fluorouracil was suggested in a noncomparative study.[43] A partial response was observed in six patients (11%) and stable disease or a minor response was observed in 13 (23%) in an early report,[43] later updated to 11% and 35%.[42] Median time to disease progression was 164 days.[42]
- In another preliminary report, a partial response of 17% (21 patients) and stable disease or a minor response of 31% (37 patients) were seen with the combination of cetuximab plus irinotecan (in the same dosage regimen previously resulting in progression),[44] later updated to 19% and 27%,[42] in 121 patients with a similar disease history. Median time to disease progression was 186 days in this noncomparative study.[42]

4. Tolerability

Adverse events were graded according to WHO criteria[45] in the six clinical trials in which cetuximab was used to treat patients with metastatic colorectal cancer expressing EGFR presented in section 3.[39-44]

- The most common adverse events reported in the BOND study were those consistent with the known safety profiles of cetuximab and irinotecan.[42] There were 186 grade 3/4 adverse events reported in this study in which 329 patients were treated with cetuximab alone or in combination with irinotecan;[42] tolerability data (figure 4) are reported in two abstracts.[42,46]
- The most common grade 3/4 adverse events occurring in patients receiving cetuximab monotherapy were acne-like rash (incidence 5.2–16%),[42,43] asthenia (7–10.4%),[42,43] abdominal pain (5.2%),[42] nausea/vomiting (4.3%)[42] and hypersensitivity reaction (3.5%).[42,43]
- Grade 3/4 toxicity reported by patients receiving cetuximab in combination with irinotecan-based chemotherapy regimens[39-42,44] was similarly heterogeneous, and included diarrhoea (approximate incidence 4–33%),[39-42] asthenia (13.7%),[42] leuco-

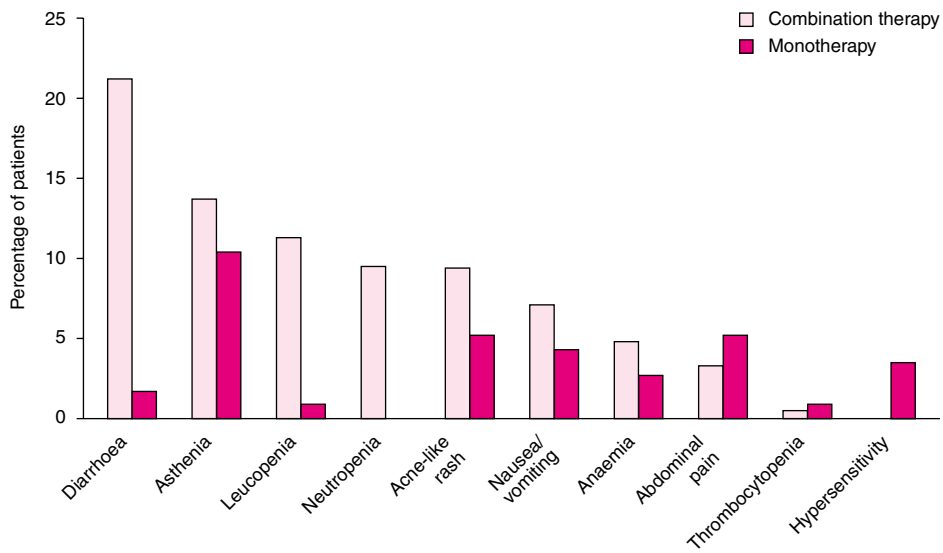

Fig. 4. Tolerability of cetuximab. Incidence of grade 3/4 adverse events in patients with irinotecan-refractory, epidermal growth factor receptor-positive, metastatic colorectal cancer in the Bowel Oncology with Cetuximab Antibody study.[42] Tolerability of cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly administered by intravenous infusion alone (n = 111) or in combination with irinotecan (125 mg/m^2 weekly, 180 mg/m^2 every 2 weeks or 350 mg/m^2 every 3 weeks; n = 218). Results are from a large, randomised, multicentre, open-label trial in patients who experienced progressive disease during or ≤12 weeks after treatment with irinotecan-based chemotherapy published as two abstracts.[42,46]

penia (11.3%),[46] rash (8–19%)[40-42,44] and neutropenia (4–33%);[39,40,42] hypersensitivity reactions occurred in 0–4% of patients.[39,42,44]

- Acneiform skin rash was the most common adverse effect associated with cetuximab therapy, with a >60% incidence reported in the majority of trials.[39-41,44] The rash was predominantly on the face and upper torso,[40] improved with continued treatment[40] and was reversible.[41] This adverse effect has been described with cetuximab previously[47-49] and is thought to be due to its interference with the physiological role of EGF in the epidermis.[47,48]
- Dose-limiting toxicity, reported in two studies, occurred in 13% and 16% of patients receiving cetuximab plus irinotecan, folinic acid and fluorouracil.[39,41] In both studies, these adverse events occurred in the group receiving the higher dose of fluorouracil and included diarrhoea,[39,41] neutropenia[39] and allergic reaction.[39] Dose modifications were required in many patients receiving this regimen.[39-41]

5. Dosage and Administration

The same dose of cetuximab was used in all of the studies presented in section 3: an initial dose of 400 mg/m^2 followed by 250 mg/m^2 administered weekly.[39-44] Cetuximab is administered by intravenous infusion, and clinical trials and expert opinion suggest that the initial dose should be administered over 120 minutes and the weekly dose over 60 minutes.[43,50] The administration of a 20mg test dose prior to the initial dose was documented in one trial[43] and has been suggested by several authors to allow early detection of allergic reactions.[50,51] Patients should be monitored for signs of hypersensitivity reaction during and for 60 minutes after each infusion.[50] Prophylactic antihistamine therapy and increased infusion time may prevent subsequent reactions.[49]

6. Cetuximab: Current Status

Cetuximab is a chimeric monoclonal antibody that selectively targets the EGFR on colorectal cancer tumour cells and induces beneficial cellular responses that increase tumour sensitivity to radiotherapy and chemotherapeutic agents. Cetuximab is licensed in Switzerland for use in combination with irinotecan for the treatment of colorectal cancer refractory to standard chemotherapy with irinotecan,[52] and is in the 'preregistration phase' of licensing in the EU and US. Superior efficacy in irinotecan-refractory metastatic colorectal cancer expressing EGFR has been indicated with cetuximab plus irinotecan compared with cetuximab alone. Preliminary results in treatment-naive patients with metastatic colorectal cancer expressing EGFR also indicate efficacy for cetuximab in combination with irinotecan, folinic acid and fluorouracil.

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