Challenges in the Use of Epidermal Growth Factor Receptor Inhibitors in Colorectal Cancer

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Key Words. Epidermal growth factor receptor • Monoclonal antibody • Cetuximab • Panitumumab • Rash • Tyrosine kinase inhibitors

LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Describe the activity of EGFR inhibitors in metastatic colorectal cancer.
2. Discuss planned studies.
3. Discuss adverse events of EGFR inhibitors.

ABSTRACT
Novel targeted agents increase the therapeutic armamentarium in metastatic colorectal cancer (mCRC). Monoclonal antibodies against the epidermal growth factor receptor (EGFR) are active against EGFR-expressing mCRC that is refractory to irinotecan. EGFR monoclonal antibodies also have promise in less advanced stages of CRC. Cetuximab and panitumumab are clearly active agents. It has been shown that cetuximab is more active when administered in combination with irinotecan. Phase II studies also report promising activity when monoclonal antibodies against the EGFR are combined with classic chemotherapeutic regimens in the first-line treatment of mCRC. However, the best means of scheduling such agents and integrating them with each other and with chemotherapy have yet to be established. The management of toxicity (particularly rash) and finding appropriate means of selecting patients pose additional challenges. While the occurrence of rash is associated with greater likelihood of response, EGFR staining by immunohistochemistry at baseline is not. For reasons that are not yet clear, the tyrosine kinase inhibitors of EGFR seem less effective than their monoclonal antibody counterparts in the therapy of mCRC. The Oncologist 2006;11:1010–1017

INTRODUCTION
Grothey et al. demonstrate that median overall survival (OS) in clinical trials correlates highly ($p = .0008$) with the percentage of patients who receive all three of the cytotoxic agents 5-fluorouracil (5-FU), oxaliplatin, and irinotecan in the course of their disease [1]. When 80%–90% of patients have had all three drugs, a median OS of more than 20 months can be expected. It is reasonable to suggest (and indeed there is already preliminary evidence) that this relationship will continue to hold with the incorporation into therapy of agents targeted against epidermal and vascular endothelial growth factors or their receptors.
Activity in Advanced Disease

In Chemoresistant Disease
The activity of epidermal growth factor receptor (EGFR) inhibitors, particularly the monoclonal antibodies (MoABs), has been established in patients with chemorefractory colorectal cancer (CRC). Figure 1 shows a simplified mechanism of action of the MoABs and tyrosine kinase inhibition of EGFR [2-5].

Saltz et al. reported a response rate (RR) of 19% and stable disease (SD) in 27% of 121 irinotecan-refractory patients treated with irinotecan plus cetuximab [6]. The same group found an 11% RR and 35% SD in 57 patients with irinotecan-refractory disease given cetuximab alone [7]. Cetuximab single agent was also given to 346 patients whose disease was refractory to both irinotecan and oxaliplatin, producing an RR of 12% and SD rate of 32% [8]. Panitumumab single agent produced a 10% RR and 38% rate of SD in 148 patients with disease resistant to irinotecan or oxaliplatin or both [9]. The median duration of response was 5.2 months (95% confidence interval [CI], 4.5–7.5 months), the median progression-free survival (PFS) was 2.0 months (95% CI, 1.9–3.8 months), and the median survival amounted to 7.9 months (95% CI, 5.7–9.9 months) [9]. Only one patient treated with panitumumab experienced an infusion-related reaction, which did not result in discontinuation of panitumumab. Skin rash was generally mild to moderate and rarely resulted in discontinuation of panitumumab. Results suggested a potential relationship between disease response and rash, although no definitive conclusions can be drawn. No clear relationship between disease response and EGFR staining intensity was evident in this study [9]. The pharmacokinetics of panitumumab appeared to reach steady state after eight doses, with no unusual accumulation up to 35 weeks after the first dose [9].

The consistent RR of 10% (or slightly greater) and the 30%–40% rate of SD achieved by EGFR inhibitors in these refractory patients are impressive.

The original work by Saltz et al. justified the BOND study, a large (329 patients) randomized phase II study of cetuximab plus irinotecan (218 patients) versus cetuximab alone (111 patients) in irinotecan-refractory CRC [10]. The RR with the combination was significantly higher, i.e., 23% versus 11% with cetuximab alone (p = .007), and the disease control rates were 56% versus 32%, respectively. The median time to progression (TTP) was also significantly greater for the combination arm (4.1 vs. 1.5 months, p < .001), and the median survival time was 8.6 months for cetuximab plus irinotecan and 6.9 months in the cetuximab arm (p = .48). The combination arm had more frequent adverse events, but the severity and incidence were similar to those anticipated with irinotecan alone.

A large phase III trial (study 408) has randomized almost 500 patients with oxaliplatin- and irinotecan-refractory EGFR-expressing metastatic CRC (mCRC) between Best Supportive Care (BSC) and BSC plus panitumumab. The aim of this pivotal trial is to show a significant difference in PFS. The results will be reported in 2006.

First-Line Therapy
In first-line therapy, there are only relatively small phase II studies, but data from five trials (none yet published in full) suggest promising activity when cetuximab is combined with either irinotecan- or oxaliplatin-based chemotherapy (Table 1) [11-15].

Thus, Rosenberg et al. reported a 48% RR and 41% rate of SD in 29 patients treated with irinotecan/bolus 5-FU/leucovorin (IFL) plus cetuximab [11]. Folprecht et al. cite a 67% RR and 29% rate of SD in 21 patients who received the German AIO (Association of Medical Oncology of the German Cancer Society) regimen of IFL plus the antibody [12]. And Rougier et al. reported a 43% RR and 45% rate of SD in a total of 42 patients treated at their higher dose level of irinotecan/5-FU/leucovorin (FOLFIRI) plus cetuximab [13].

Turning to oxaliplatin-containing regimens, Van Cutsem et al. found an 81% RR (74% confirmed responses) in 42 patients given cetuximab with oxaliplatin/5-FU/leucovorin (FOLFOX) in the ACROBAT study [14]. Of these patients, 23% subsequently had their liver metastases resected. Hoehler et al. reported a 55% RR and SD rate of 24% in 38 patients given cetuximab plus 5-fluorouracil/leucovorin/oxaliplatin (FUFOX) [15].

There are also data showing good activity first line when panitumumab (ABX-EGF) is added to IFL (Table 2) [16]. Of 19 patients, 47% had an RR and disease was stable.
The rate of early disease progression, which happened in only one patient in this small trial, was low. All patients who responded to the panitumumab combination developed a skin rash.

**In Combination with Other Novel Agents**

Animal models suggest that additive efficacy and sometimes synergy can be achieved using EGFR inhibitors in combination with agents that inhibit the vascular endothelial growth factor receptor [17, 18].

There is therefore good preclinical rationale for the BOND2 study of cetuximab plus bevacizumab with or without irinotecan in irinotecan-refractory CRC patients not tested for the presence of the EGFR [10, 19, 20]. In a randomized phase II study, irinotecan-refractory CRC patients received irinotecan (same dose and schedule as per their last treatment administration prior to study) plus cetuximab (400 mg/m² loading dose, then weekly at 250 mg/m²) plus bevacizumab (5 mg/kg given every other week) versus cetuximab (400 mg/m² loading dose, then weekly at 250 mg/m²) plus bevacizumab (5 mg/kg given every other week) [19]. Use of the two antibodies plus irinotecan (n = 41) is associated with a 37% RR and 7.9-month TTP, compared with an RR of 20% and 5.6-month TTP in patients treated with cetuximab plus bevacizumab alone (n = 40). In the BOND study, the cetuximab/irinotecan arm achieved an RR of 23% and the TTP was 4.1 months, while the cetuximab alone arm had an RR of 11% and a TTP of 1.5 months [10]. In the Saltz et al. study [19], no unexpected toxicities were encountered. Grade 3 rash and grade 2 rash were observed in 7 (17%) and 25 patients (60%), respectively, on the cetuximab/bevacizumab/irinotecan arm and in 8 (20%) and 26 patients (65%), respectively, on the cetuximab/bevacizumab arm. Grade 3–4 diarrhea was observed in 24% of patients on the cetuximab plus bevacizumab alone, while on the cetuximab/bevacizumab/irinotecan arm and 0% of patients on the cetuximab/bevacizumab arm. The combination of cetuximab/bevacizumab, alone or with irinotecan, appeared tolerable and active and warrants the investigation of this combination in front-line combination chemotherapy regimens.

**Table 1. First-line phase II studies in EGFR-expressing metastatic colorectal cancer with cetuximab in combination with either irinotecan- or oxaliplatin-based chemotherapy [11–15]**

<table>
<thead>
<tr>
<th>Irinotecan-based chemotherapy</th>
<th>Oxaliplatin-based chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients</strong></td>
<td></td>
</tr>
<tr>
<td>AIO + cetuximab [12]</td>
<td>FOLFOX + cetuximab [14]</td>
</tr>
<tr>
<td>FUFOX + cetuximab [15]</td>
<td></td>
</tr>
<tr>
<td><strong>CR + PR</strong></td>
<td></td>
</tr>
<tr>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>67%</td>
<td>81%</td>
</tr>
<tr>
<td>43%</td>
<td>55%</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>29–68</td>
<td>26–66</td>
</tr>
<tr>
<td>47–87</td>
<td>61–88</td>
</tr>
<tr>
<td>41%</td>
<td>45%</td>
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<tr>
<td>29%</td>
<td>17%</td>
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<tr>
<td>45%</td>
<td>24%</td>
</tr>
<tr>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Remarks</strong></td>
<td></td>
</tr>
<tr>
<td>Two dose levels; RR in level 2</td>
<td>23% resection of liver metastases</td>
</tr>
</tbody>
</table>

**Table 2. Panitumumab in EGFR-expressing metastatic colorectal cancer: first-line trials [16]**

<table>
<thead>
<tr>
<th>Irinotecan-based chemotherapy</th>
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</thead>
<tbody>
<tr>
<td>IFL + panitumumab [16]</td>
</tr>
<tr>
<td><strong>Total patients</strong></td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td><strong>Complete response + partial response</strong></td>
</tr>
<tr>
<td>47%</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
</tr>
<tr>
<td>32%</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
</tr>
<tr>
<td>5% (One patient)</td>
</tr>
<tr>
<td><strong>Remarks</strong></td>
</tr>
<tr>
<td>One patient with complete response; all patients with skin rash</td>
</tr>
</tbody>
</table>

Abbreviations: AIO: irinotecan/5-fluorouracil/folinic acid; CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; FOLFIRI, irinotecan/5-fluorouracil/leucovorin; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; FUFOX, 5-fluorouracil/leucovorin/oxaliplatin; IFL, irinotecan/5-fluorouracil/leucovorin; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.
ONGOING STUDIES

The CRYSTAL study is a large multicenter study in which 1,212 patients with previously untreated mCRC that expresses EGFR have been randomized to FOLFIRI with or without the addition of cetuximab (Fig. 2). This should provide important information on the role of EGFR inhibition first line.

The ongoing United Kingdom Medical Research Council’s COIN phase III trial in mCRC will randomize approximately 2,400 first-line patients, whose EGFR status has not been established, to one of three arms: continuous oxaliplatin and fluoropyrimidine chemotherapy, the continuous chemotherapy plus cetuximab, or chemotherapy for 12 weeks followed by its interruption and resumption on disease progression (Fig. 3). The Cancer and Leukemia Group B (CALGB) 80405 plans to randomize 2,289 patients in the first-line treatment of mCRC between chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab or cetuximab or the combination of bevacizumab plus cetuximab (Fig. 4). The PACE is a multicenter trial in the U.S. in which more than 1,000 patients will be randomized in the first treatment of mCRC between chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab ± panitumumab.

Neoadjuvant and Adjuvant Therapy

In the neoadjuvant setting, early reports of small phase II studies suggest that high rates of resection are achieved when surgery is preceded by an EGFR inhibitor combined with chemotherapy. The resectability rate of 23% in the ACROBAT study has to be confirmed in larger studies [14]. However, trials such as the CECOG EMR 62202-612 study now under way in central Europe, in which patients with EGFR-expressing mCRC and initially unresectable liver metastases are randomized to FOLFOX4 plus cetuximab or FOLFIRI plus cetuximab (planned number of patients is 50 per study arm), should provide an indication of what may be achievable in the neoadjuvant setting.

The BOS study of the European Organization for Research and Treatment of Cancer will randomize patients with resectable liver metastases of CRC preoperatively to FOLFOX4 plus cetuximab versus FOLFOX4 plus cetuximab and bevacizumab. The outcome of this trial should provide a basis for the strategy of developing a neoadjuvant and adjuvant treatment.

The CALGB has another strategically important trial. In this study, patients who have received FOLFOX or FOLFIRI first line are being randomized to cetuximab alone, bevacizumab alone, or their combination (Fig. 4).

Studies in the adjuvant setting, and of novel agents combined with radiotherapy in rectal cancer, have also started, and many are being planned.

CHALLENGES OF SCHEDULING AND TOXICITY

The optimal dose of EGFR inhibitors is not clear: in particular, we do not yet know whether the best option is to dose until the appearance of rash. The possibility of twice weekly, rather than once weekly, dosing needs to be explored with cetuximab.

Figure 2. Phase III study of FOLFIRI ± cetuximab in metastatic CRC: CRYSTAL study design. Abbreviations: 5-FU, 5-fluouracil; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FOLFIRI, irinotecan/5-fluorouracil/leucovorin; LV, leucovorin.

Figure 3. ‘COIN’ phase III study in first-line metastatic colorectal cancer: study design. Abbreviations: CT, chemotherapy; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer.
The Incidence and Significance of Rash

Figure 5 shows a typical EGFR inhibitor–induced skin rash. The BOND study showed that the most frequent adverse events related to cetuximab are allergic reaction and skin toxicity [10]. However, cetuximab did not increase the incidence of those side effects typically seen with irinotecan.

In the study of panitumumab by Hecht et al., 95% of patients experienced rash of any grade [9]. However, the rash was grade 3 in only 3% of patients and none experienced grade 4 rash. Only one of 148 patients had an infusion-related reaction (grade 3) despite the fact that the antibody was generally administered without premedication. That patient then received a premedication, and dosing with panitumumab was not interrupted. In 110 patients tested to date, none has shown formation of human antihuman antibody.

The association between rash and efficacy is proving intriguing. Retrospective analysis of the BOND data showed a clear association between higher grades of skin reaction and RR and median TTP [10]. This was true also for OS, the median value rising from 3 months in patients with no rash to 14 months in those with rash of grade 3 severity. The same relationship was seen in the panitumumab study [9]. The association between rash severity and survival seems to hold true across the range of clinical trials of cetuximab in CRC, and indeed in the treatment of tumors at other disease sites (Fig. 6) [7, 10, 21–24]. Figure 7 describes severe EGFR inhibitor–induced skin reactions and provides therapy suggestions [25].

However, the fact that all of these analyses are retrospective suggests these data should be treated with caution. They should certainly not be made the basis of any decision by regulatory authorities to restrict continued dosing with EGFR inhibitors to patients showing a rash.

In this context, the current EVEREST study will provide food for thought. In the trial, patients with irinotecan-refractory EGFR-expressing CRC receive 3 weeks of classic treatment with cetuximab and irinotecan (Fig. 8). At 3 weeks, those who do not have grade 2 or greater rash are randomized to continue with the standard regimen or to a dose escalation of cetuximab until severe rash occurs. Serial skin and tumor biopsies for expression of EGFR and markers of downstream signaling should help elucidate the link between rash and antitumor activity.

The management of EGFR inhibitor rash and the associated postinflammatory changes is another challenge. Although randomized trials on the optimal patient management are lacking, the experience with topical treatments and with tetracyclines is growing and experience-based treatment advices are given [25].

Figure 4. Schema of the Cancer and Leukemia Group B 80405 phase III study in advanced CRC. Abbreviations: CRC, colorectal cancer; FOLFIRI, irinotecan/5-fluorouracil/leucovorin; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin.

Patient Selection

While EGFR expression is evident on immunohistochemistry in 70%–80% of CRCs, data from the BOND study show that intensity of staining does not correlate with RR [10]. The panitumumab study involved an initial cohort of patients who were EGFR ++ or EGFR +++ in 10% or more of evaluated cells, and a later cohort of patients with less intense staining. The two cohorts seem not to differ appreciably in rates of response or stable disease [9].

Figure 5. Epidermal growth factor receptor (EGFR) inhibitor–induced rash [25].
These findings may relate to the absence of a correlation between the EGFR status of the primary tumor and that of metastases [26]. More recently, Chung et al. have reported a 25% rate of response in 16 patients retrospectively identified as negative by immunohistochemistry for EGFR [27]. No one has yet established a marker that is genuinely valuable in predicting response to EGFR inhibitors in patients with CRC. For example, there appears to be no equivalent of the EGFR mutation that seems to mediate response to gefitinib in patients with lung cancer.

Figure 6. Correlation of rash and survival after treatment with cetuximab [7, 10, 21–24]. Abbreviations: CRC, colorectal cancer; SCCHN, squamous cell carcinoma of the head and neck.

Figure 7. Epidermal growth factor receptor (EGFR) inhibitor–induced skin reactions and therapy suggestions. (Picture kindly provided by S. Segaert.)
EGFR Tyrosine Kinase Inhibitors in CRC

Compared with the anti-EGFR MoABs, the role of tyrosine kinase inhibitors of EGFR has not been extensively investigated in mCRC. However, it seems clear that gefitinib as a single agent is not active in chemorefractory CRC [28, 29]. In combination with FOLFOX, gefitinib does have a high RR (78% first line), but toxicity is also high, with grade 3–4 diarrhea occurring in 49% of patients [30]. The combination of erlotinib with capecitabine and oxaliplatin is more feasible but less active [31]; and FOLFOX plus the EGFR tyrosine kinase inhibitor EKB-569 also seems feasible [32].

Conclusion

The novel targeted agents increase the therapeutic armamentarium in mCRC. The MoABs cetuximab and panitumumab against EGFR have proven activity against EGFR-expressing irinotecan-refractory mCRC. Furthermore, EGFR MoABs have promising activity in less advanced stages of CRC. Cetuximab and bevacizumab have appealing activity when combined.

Disclosure of Potential Conflicts of Interest

The author indicates no potential conflicts of interest.

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