Cetuximab: clinical results in colorectal cancer

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In recent years, the introduction of targeted therapies into clinical practice seems to offer incremental benefits in the treatment of metastatic colorectal cancer (mCRC), mainly when they are employed in combination with optimal chemotherapy and/or radiotherapy. In this paper, we focus on Cetuximab and its role in the treatment of mCRC.

Key words: Cetuximab, colorectal cancer

**Introduction**

Growth factors and their receptors are vital to normal cellular dynamics as they regulate cellular growth, proliferation, differentiation, migration, angiogenesis and cell death.

Six subclasses of tyrosine kinase receptors have been isolated and fully characterized. They include receptors for the following unique ligands: (i) insulin, (ii) platelet-derived growth factors, (iii) epidermal growth factor (EGF), (iv) fibroblast growth factor, (v) ephrins and (vi) growth hormone [1]. The EGF family consists of four transmembrane receptors, including epidermal growth factor receptor (EGFR) (HER1/erbB-1), HER2 (erbB-2/neu), HER3 (erb-3) and HER4 (erbB-4) [2]. Cetuximab is a chimeric mouse–human monoclonal antibody (mAb) targeting the extracellular domain of the EGFR, thereby preventing the binding of its natural ligand (EGF and transforming growth factor α) and triggering the internalization of the receptor [3].

In head and neck cancer, the vast majority of tumors are strongly EGFR-positive; EGFR gene expression occurs in 25% to 77% of colorectal neoplasms [4, 5]. In some studies, the overexpression has been correlated with disease progression, poor prognosis and reduced sensitivity to chemotherapy [6]. Several strategies have been developed to target EGFR including mAbs and small molecules tyrosine kinase inhibitors [2, 7].

In this paper, we focus on Cetuximab and its role in the treatment of metastatic colorectal cancer (mCRC).

**Colorectal cancer**

**Previously treated patients**

Three nonrandomized and one randomized trial (BOND study, single arm) evaluated the efficacy of single-agent Cetuximab in previously treated mCRC patients expressing the EGFR [8–11]. The results of these studies were similar in terms of objective response rate (RR), disease control, median time to progression (TtP) and median overall survival (OS) and ranged from 8% to 12%, 32% to 50%, 1.4 to 4.2 months and 6.4 to 7.0 months, respectively.

In the Lenz study [9], nine erroneously EGFR-negative patients were enrolled: two objective responses were observed indicating that the recommended practice of testing EGFR status by immunohistochemistry to select for Cetuximab therapy seems to be inappropriate and other predictive tests are needed.

Preclinical studies [12] demonstrated synergistic tumor growth inhibition or tumor regression when Cetuximab was administered in combination with Irinotecan (CPT-11). A randomized phase II trial (BOND study) compared Cetuximab + CPT-11 with Cetuximab alone in previously treated mCRC patients 11. In this study, 329 EGFR-positive patients with progressive disease during or within 3 months after treatment with an Irinotecan-based regimen were randomized to receive either Cetuximab (400 mg/m² loading dose, followed by 250 mg/m² weekly) + CPT-11 (same schedule as before) or Cetuximab alone. The intent-to-treat analysis showed a statistically significant higher overall RR (23% versus 11%, \(P = 0.007\)) and disease control (56% versus 32%, \(P < 0.001\)) with a longer TtP (4.1 versus 1.5 months, \(P < 0.001\)) in favor of the combination arm. The median OS was also longer for Cetuximab + CPT-11 (8.6 versus 6.9 months) but this difference was not statistically significant (\(P = 0.48\)). This may be due mainly to two reasons: firstly the study was not powered to demonstrate a survival benefit and secondly that patients could switch from the monotherapy to the combination arm at disease progression. Furthermore, in this study, EGFR positivity was not related with results, while patients with severe skin toxicity (grade >3) obtained better RR and OS than cases with lower grade.

In the Monoclonal Antibody Erbitux in a European Pre-licensure trial [13], the BOND study results of the combination arm were confirmed: 20% RR and a median OS of 9.2 months were observed in 1147 Irinotecan-refractory mCRC patients. The progression-free survival and the OS at 12, 24, 36 and
48 weeks were 61%, 34%, 17% and 6% and 68%, 39%, 22% and 16%, respectively.

Recently, a randomized phase III trial concluded the accrual: the European Prospective Investigation into Cancer and Nutrition (EPIC) study investigated the activity of Cetuximab + CPT-11 versus CPT-11 alone in patients previously treated with Oxaliplatin-based regimens. Preliminary results on the safety analyses concerning the first 400 patients showed data similar to those of previous experiences [14].

Considering these data, Cetuximab in combination with CPT-11 has been registered in the United States and Europe for the treatment of mCRC patients expressing the EGFR after failure of Irinotecan-prior cytotoxic therapy.

Furthermore, preclinical studies [15] demonstrated that Cetuximab reduces the level of the vascular endothelial growth factor, basic fibroblast growth factor and interleukin-8. In a randomized phase II trial (BOND-2 study), patients previously treated with Irinotecan received Cetuximab + Bevacizumab + CPT-11 or Cetuximab + Bevacizumab alone [16]. Seventy-four patients were assessable (39 and 35 in each arm); a RR of 38% versus 23% and a median TtP of 8.5 versus 6.9 months were observed, respectively. The main grade 3–4 toxic effects in the three-drug combination therapy were diarrhea 26%, neutropenia 18%, fatigue 10% and skin 18%.

Following these data, two large randomized phase III trials started: the Cancer and Leukemia Group B/Southwest Oncology Group Study 80405 (FOLFIRI/FOLFOX-6 + Cetuximab or Bevacizumab or both) and the CAIRO II study (XELOX + Cetuximab + Bevacizumab or XELOX + Bevacizumab alone). These studies are still ongoing.

**first-line therapy**

Five phase II trials [17–21] evaluated the activity of Cetuximab combined with Irinotecan-based regimens. Different schedules were employed: the observed RR was in the range of 44%–67%, with a disease control ranging from 76% to 96% and a median TtP of ~10 months.

Furthermore, five phase II studies [21–25] investigated the activity of the combination of Cetuximab + FOLFOX-4. A French/Spanish trial [22] enrolled 43 patients: an objective RR of 72%, a disease control rate of 95%, a median TtP of 12.3 months and a median OS of 30 months were recently reported [23]. Interestingly, 10 patients (23%) with initially unrectsectable metastases underwent surgery with curative intent.

These data have been confirmed by a larger phase II trial from the Gruppo Oncologico dell’Italia Meridionale [23] that enrolled 70 unselected patients who were treated with the same combination. Three complete (4.5%) and 39 partial (58.2%) confirmed responses were observed in the 67 assessable patients for an overall RR of 62.7%; additionally 21 patients (31.3%) had stable disease with a disease control rate of 94%. Besides among the 33 patients with initially unrectsectable liver disease, 7 (21%) were resected after treatment. These data confirm the possibility to employ this combination in a neo-adjuvant setting.

Globally, the results of the combination of Cetuximab + FOLFOX regimens in terms of activity are in the range of 54%–72%, with a disease control of 86%–95% and a median TtP ranging from 8 to 12 months.

Data from phase III trials are waiting: the OPUS study (Cetuximab + FOLFOX to FOLFOX alone), the COIN study (Cetuximab + FOLFOX or FOLFOX alone or FOLFOX stop and go after 12 cycles) and the NORDIC VII study (continuous FLOX or continuous FLOX + Cetuximab or intermittent FLOX + continuous Cetuximab). The results of these ongoing studies will elucidate the role of these combinations in first-line treatment.

The addition of Cetuximab to Irinotecan or Oxaliplatin-based regimens did not increase the toxicity: globally, more grade 3–4 neutropenia (33% versus 21%) and neurotoxicity (16%–25% versus 0) for CPT-11 and L-OHP schedules have been, respectively, observed, while diarrhea was similar. Higher grade of skin toxic effects was observed in 6%–30% of cases of these studies.

Preliminary data from an AIO randomized phase II trial comparing irinotecan (200 mg/m²) + Capcitabine (800 mg/m² b.i.d.) + Cetuximab to Oxaliplatin (130 mg/m²) + Capcitabine (1000 mg/m² b.i.d.) + Cetuximab reported a RR of 42.4% and 65.5%, respectively (P = 0.008), with similar disease control (90.9% versus 93.1%).

**conclusion**

Results from Cetuximab studies indicate an intrinsic activity of this drug in the treatment of mCRC. Combined with Irinotecan, a well-defined role in the salvage treatment of mCRC was established. Data from phase II trials in metastatic disease seem to indicate increased results with the addition of Cetuximab to standard chemotherapy treatments (in particular, with Oxaliplatin-containing regimens). Pending data from phase III trials will clarify their role in this setting.

The possibility to include Cetuximab as adjuvant treatment is evaluated in two ongoing trials: PETACC-8 and NCCTG-147 studies. In both trials, patients with stage III colon cancer are randomized to receive FOLFOX-4 + Cetuximab or FOLFOX-4 alone.

**references**