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Clinical results of EGFR-targeted therapies in advanced colorectal cancer

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ABSTRACT

This paper is an updated review of the pre-clinical rationale and clinical results of new EGFR-targeted agents – cetuximab and panitumumab – employed in the management of advanced/ metastatic colorectal cancer. The addition of either biologic agent or last generation standard chemotherapy regimens – FOLFIRI and FOLFOX – has yielded better results as compared to those reported for chemotherapy alone. These results have been obtained without a significant increase in severe toxicity with the exception of skin side-effects.

1. Introduction

The treatment of metastatic colorectal cancer (mCRC) has significantly evolved during the last decade. Median overall survival (mOS) has been increased to about 21–22 months with the addition to fluorouracil (FU) of new anticancer drugs, such as CPT-11 (CPT-11) and OHP (OHP), and appears to be correlated with the proportion of patients receiving all three active drugs.[1] More recently, the introduction of targeted therapies seems to offer incremental benefits, mainly when they are employed in combination with optimal chemotherapy.

In this paper, we focus on clinical results obtained with the addition of Cetuximab (CET) and Panitumumab (PAN) in the treatment of mCRC.

2. Epidermal growth factor receptor (EGFR)

EGFR is a member of the HER-family kinases, which includes four closely related cell membrane receptors: EGFR (HER1 or erbB1), erbB2 (HER-2), erbB3 (HER3) and erbB4 (HER4).[2,3] These receptors are trans-membrane glycoproteins consisting of an extra-cellular ligand-binding domain, a trans-membrane domain and an intracellular domain with tyrosine kinase activity for signal transduction. The primary ligands to EGFR include mitogens, such as EGF and TGF-α, which bind to EGFR via its extra-cellular domain inducing homodimerisation or heterodimerisation. Following receptor dimerisation, activation of the intrinsic protein tyrosine kinase, tyrosine autophosphorylation occurs, initiating a cascade of intracellular mitogenic signalling and other cellular activities.[4,5]

EGFR is over-expressed in up to 70% of human colorectal tumours, and has been associated with an advanced stage of disease.[6,7] Early studies suggested that the level of EGFR over-expression was directly correlated with active prolifera-

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tion of malignant cells and poor prognosis of patients.[8] However, recent studies found no association between EGFR expression and stage or survival.[9]

3. Cetuximab

CET is a recombinant, chimeric human/murine immunoglobulin G1 that binds specifically to the human EGFR extra-cellular domain. This antibody competes with ligands for receptor binding and has a higher affinity for the receptor than either EGF or TGF-α. The antibody blocks ligand binding and induces receptor internalisation and degradation, resulting in down-regulation of surface EGFR expression.

Pre-clinical studies have shown that CET increases the anti-tumor activity of various anticancer drugs – including CPT-11 – both *in vitro* and *in vivo*. Combination treatment of CET with these drugs resulted in markedly potentiated tumour inhibition as compared with either agent alone.[10–12] The addition of CET to CPT-11, and FU/folinic acid inhibited tumour growth in more than 75% of human CRC xenograft in mouse, compared to 25% or 48% with chemotherapy alone or CET alone, respectively.[13] Furthermore, the combination of CET with OHP showed synergistic anti-tumor effect in human CRC carcinoma xenografts and reversed OHP resistance.[14,15] Similar potentiated anti-tumor activity has been observed when CET was used in combination with radiation therapy.[16]

Phase I studies showed that the most frequent adverse events were acneiform rash, fever and chill, asthenia, transminase elevation and nausea. A low rate of immunogenicity toxicity was observed, with less than 4% grades 3–4 anaphylactic adverse events.[17] Furthermore, CET administration has been recently associated with severe hypomagnesemia occurring in 23% of patients.[18]

In the previously treated patients, three non-randomised and one randomised trial evaluated the efficacy of single-agent CET in patients expressing the EGFR.[19–22] In these studies, the observed results were similar. Objective response rate (ORR) and disease control rate (DCR: CR + PR + SD), median time to progression (TTP) and mOS ranged from 8% to 12%, 32% to 50%, 1.4 to 4.2 months and 6.4 to 7.0 months, respectively. The probability of patients experiencing a response to CET was independent to the intensity of IHC staining for EGFR and the percentage of tumour cells considered EGFR positive by IHC staining.

In a randomised phase II trial (BOND study), patients with EGFR-expressing CPT-11-refractory mCRC were randomly assigned to CET + CPT-11.[22] Globally, 329 patients with progressive disease during or within 3 months after treatment with an CPT-11-based regimen were randomized in a 2:1 fashion to CET (400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly) plus CPT-11 (same schedule as before) or CET alone. A statistically significant higher ORR (23% versus 11%, $p = 0.007$) and DCR (56% versus 32%, $p < 0.001$) with a longer TTP (4.1 versus 1.5 months, $p < 0.001$) in favour of the combination arm, were observed. Median survival in the two arms was not significantly different (8.6 versus 6.9 months; $p = 0.48$), because the study was not powered to demonstrate a survival benefit and due to the allowed cross-over to combination therapy after progression on CET alone. Furthermore, in this study, EGFR positivity was not related with results, whilst patients with severe skin toxicity (grade >3) obtained better RR and OS than cases with lower grade.

The results of the combined arm of BOND study were substantially confirmed in the MABEL trial[23]: 20% ORR and a mOS of 9.2 months were observed in 1147 CPT-11-refractory mCRC patients. The PFS and the OS at 12, 24, 36 and 48 weeks resulted of 61%, 34%, 17% and 6% and 68%, 39%, 22% and 16%, respectively.

Results of the addition of CET to CPT-11 in the previously treated mCRC patients were recently confirmed in an open label, randomised phase III trial (EPIC study): 1298 progressive patients after fluoropyrimidine and OHP failure were randomly assigned to CPT-11 + CET. In this trial, a statistically significant higher ORR (16.4% versus 4.2%, $p < 0.0001$), DCR (61.4% versus 45.8%, $p < 0.0001$) and PFS (4.0 versus 2.6 months, $p < 0.0001$) in favour of the combination arm were observed. Median OS in the two arms was not significantly different (10.7 versus 10.0 months; $p = 0.71$), due to the allowed cross-over to combination therapy after progression on CPT-11 alone.[24]

In a recent study, 40 mCRC patients refractory or resistant to OHP were treated with the combination of CAPOX plus CET obtaining an ORR of 20% and a DCR of 47.5%, with minimal toxicity. Furthermore, 21 patients progressive to CAPOX plus CET were treated with CPT-11 plus CET with an ORR of 9.5%, a DCR of 38% and a TTP of 3.7 months suggesting. that some patients could benefit from a 'sequential approach'.[25]

Pre-clinical studies demonstrated that CET reduce the level of VEGF, basic fibroblast growth factor and interleukin-8.[26] Advanced CRC patients previously treated with CPT-11 received in a randomised phase II trial (BOND-2 study) CET + bevacizumab + CPT-11 (CBI) or CET + bevacizumab (CB) alone.[27] An ORR of 37% versus 20%, a median TTP of 7.3 versus 4.9 months, and a median OS of 14.5 versus 11.4 months were observed, respectively, in CBI and CB arms. The main grade 3–4 toxicities in the three-drug combination therapy were diarrhoea 28%, neutropenia 23%, fatigue 9% and skin 21%.

Following these data, two large randomised phase III trials started: the CALGB/SWOG 80405 study (FOLFIRI/FOLFOX-6 plus CET or Bevacizumab or both) and the CAIRO-2 study (XELOX + CET + Bevacizumab or XELOX + Bevacizumab alone). These studies are still ongoing. However, an interim analysis of toxicity in the CAIRO-2 study demonstrated that the addition of CET to the XELOX-bevacizumab therapy appeared to be safe and feasible.[28]

In first-line therapy, CET alone was administered to 39 patients in a phase II trial: 1 CR, 3 PR and 13 SD were obtained with an ORR of 10% and a DCR of 44%.[29] Better results were observed with the addition of CET to standard combination chemotherapy. Phase II trials[30–33] evaluated the activity of CET combined with CPT-11-based regimens. ORR was in the range of 42–67%, with a DCR ranging from 86% to 96% and a median TTP of about 10 months (Table 1). Preliminary results of a phase III trial (CALGB 80203) confirmed these results.[34] Data from the largest phase III trial comparing FOLFIRI + CET in 1217 patients (CRYSTAL study) showed that the primary end-point (PFS) was met: 8.9 months with the addition of CET versus 8.0 months in the FOLFIRI arm alone ($p = 0.0479$).

Table 1 – CET plus CPT-11-containing regimens in first-line therapy of mCRC patients

Author (Ref.)	Phase study	CET+	No. of pts	ORR (%)	DCR (%)	Median (months) TTP	Median (months) OS
Rosenberg[30]	II	IFL	27	44	nr	nr	nr
Rougier[31]	II	FOLFIRI	22	46	86	10.9	nr
Folprecht[32]	II	CPT-11+FA-FU	21	67	95	9.9	33
Heinemann[33]	II	XELIRI	33	42	91	nr	nr
Venook[34]	III[a]	FOLFIRI	59	42	nr	nr	nr
Van Cutsem[35]	III	FOLFIRI	608	47	nr	8.9	nr

nr: not reported.
a Preliminary results.

ORR also was significantly in favour of the combination treatment (46.9% versus 38.7, $p = 0.0038$)[35], such as PFS duration in the subgroup of patients with only liver involvement (11.4 versus 9.2 months). These benefits were not associated with greater toxicity, with the exception of skin toxicity.

As shown in Table 1, the activity of the combination of CET with OHP-containing regimens was investigated in phase II studies.[36–40] Different schedules were employed: the observed ORR was in the range of 53–72%, with a DCR ranging from 82% to 95% and a median TTP ranging from 8 to 12.3 months (see Table 2).

A French/Spanish trial[39] enrolled 43 patients: an ORR of 72%, a DCR of 95%, a median TTP of 12.3 months and a median OS of 30 months were recently reported.[39] Interestingly, 10 patients (23%) with initially unresectable metastases underwent surgery with curative intent. These data have been confirmed by a larger phase II trial from the GOIM[40] that enrolled 70 unselected patients who were treated with the same combination. Updated data of this study showed 4 complete (6%) and 39 partially (58.2%) confirmed responses observed in the 67 evaluable patients for an ORR of 64.2%; additionally, 20 patients (29.8%) had stable disease (SD) with a DCR of 94%. In the group of the 33 patients with initially unresectable liver disease, radical resection of disease after treatment was obtained in 7 cases (21%). Data from these studies confirm the possibility to employ this combination in a neoadjuvant setting.

A large phase II trial (OPUS study)[41] compared FOLFOX4 alone versus the combination of FOLFOX4 with CET in 367 patients, with ORR as the primary end-point. ORR was higher in the CET arm (45.6% versus 35.7%).

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

The possibility to include CET as adjuvant treatment is evaluated in the two ongoing trials: the PETACC-8 and the NCCTG-147 studies. In both trials, patients with stage III CRC are randomised to receive FOLFOX-4 plus CET or FOLFOX-4 alone. The planned enrolment is 2000 and 2300 patients.

4. Panitumumab

PAN is a fully human monoclonal antibody against EGFR, the same target of CET.[42] One of the main differences between PAN and CET pertains to the immunoglobulin G (IgG) backbone of the antibody. CET is a chimeric mouse × human monoclonal antibody of the IgG1 class; PAN, in contrast, is a fully human monoclonal IgG2 antibody. The different IgG back bones could conceivably affect the pharmacokinetic as well as the pharmacodynamic and safety characteristics of these two drugs.

Phase II studies confirmed the efficacy of single-agent PAN in patients with CPT-11-refractory mCRC with ORR around 10%, such as CET in the same setting. As with CET, the probability of experiencing a response was independent to the intensity of IHC staining for EGFR and the percentage of tumour cells considered EGFR-positive by IHC.[43–45]

Table 2 – CET plus OHP-containig regimens in first-line therapy of mCRC patients

Author (Ref.)	Phase study	CET+	No. of ORR pts	DRC (%)	DRC (%)	Median (months) TTP	Median (months) OS
Seufferlein[36]	I/II	FUFOX	49	54	nr	nr	nr
Dakhil[37]	II	FOLFOX	82	61	90	8	nr
Venook[34]		FOLFOX	58	55	nr	nr	nr
Borner[38]	II	XELOX	37	53	82	nr	nr
Heinemann[33]	II	XELOX	29	66	93	nr	nr
Tabernero[39]	II	FOLFOX4	43	72	95	12.3	30.0
Colucci[40a]	II	FOLFOX4	67	64	94	nr	nr
Bokemeyer[41]	II	FOLFOX4	169	46	85	nr	nr

nr: not reported.
a Updated data.

The most important clinical study showing the efficacy of PAN was a phase III trial that randomized patients with chemotherapy-refractory mCRC (all patients received 5-FU, CPT-11 and OHP) to receive 6 mg/kg PAN plus best supportive care (BSC) ($n = 231$) every 2 weeks or BSC alone ($n = 232$), with the option to crossover to another trial and receive PAN at the documented progression of disease. Patients who received PAN every 2 weeks showed a 46% decrease in tumour progression rate versus those who received BSC. A significantly higher proportion of patients were alive and progression-free on PAN at all the scheduled time points through week 32. PAN also significantly improved DCR (36% versus 10%). The independently evaluated ORR was 8% with PAN versus 0% with BSC alone, and the median duration of response was 17 weeks. The SD rate was 28% with PAN versus 10% with BSC. The ethically crossover option to active treatment made it possible for the trial to assess the effect of PAN on mOS, since most patients (75%) gained access to it. The results of this trial clearly document the efficacy and clinical benefit of patients receiving single agent PAN as a salvage therapy.[46] *KRAS* status was evaluated in patients who received either PAN plus BSC, or BSC alone.[47] The primary objective of this study was to examine whether the efficacy of PAN on PFS was significantly greater in patients with wild-type *KRAS* than in those with tumours containing the mutated gene.

The cohort consisted of 427 patients in whom *KRAS* status was known. Of this group, 43% had a mutated *KRAS* gene and 57% had wild-type *KRAS*. The cohort was almost evenly divided between those receiving PAN plus supportive care ($n = 206$) and those receiving best supportive care alone ($n = 219$). They found that median PFS for patients treated with PAN who had wild-type *KRAS* was 12.3 weeks; for those with the mutated gene, median PFS was 7.4 weeks. The median PFS for patients in both *KRAS* groups who received best supportive care only was 7.3 weeks. Amongst patients with wild-type *KRAS* who were treated with PAN, we observed an ORR of 17%, and 34% of cases had stable disease. Amongst patients with the mutated *KRAS* gene, 0% responded and 12% had stable disease. When the two treatment groups were combined, the OS was longer in patients with wild-type *KRAS* than in those with mutated *KRAS* [8].

Several international trials are now ongoing to assess the efficacy of PAN in association with standard chemotherapy in mCRC. The randomized phase III trial PACCE (PAN Advanced Colorectal Cancer Evaluation), investigating the use of PAN combined with bevacizumab as an add-on to FOLFOX or FOLFIRI in the first-line setting, has been discontinued based on a preliminary review of data from a pre-planned interim efficacy analysis scheduled after the first 231 events. This analysis revealed a statistically significant difference in PFS in favour of the control arm. An unplanned analysis of OS also demonstrated a statistically significant difference favouring the control arm.

The 'PRIME' or '203' trial (PAN Randomized trial in combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) is a phase III trial investigating PAN in combination with FOLFOX as a first-line treatment. Patients enrolled in the study are randomized to receive FOLFOX4 + PAN 6.0 mg/kg once every 2 weeks. The primary end-point is PFS and other end-points include OS, ORR, TTP, duration of response and safety.

The '181' trial is a phase III trial investigating PAN in combination with FOLFIRI chemotherapy as a second-line treatment. Patients enrolled in the study are randomized to receive FOLFIRI + PAN 6.0 mg/kg. The co-primary end-points are PFS and OS, other end-points include ORR, TTP, duration of response and safety. The results of this studies and new randomized trials will reveal the real rule of PAN in mCRC therapy.

5. Conclusions

Results from CET studies indicate an intrinsic activity of this drug in the treatment of mCRC. Combined with CPT-11, 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 CET to standard chemotherapy treatments (in particular, with OHP-containing regimens). Pending data from phase III trials will clarify its role in this setting.

Conflict of interest statement

None declared.

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