A triplet combination with irinotecan (CPT-11), oxaliplatin (LOHP), continuous infusion 5-fluorouracil and leucovorin (FOLFOXIRI) plus cetuximab as first-line treatment in KRAS wt, metastatic colorectal cancer: a pilot phase II trial

**Keywords:** FOLFOXIRI; cetuximab; metastatic colorectal cancer

Colorectal cancer (CRC) remains a major health problem with an estimated 143,397 new cases and 51,690 deaths occurring in 2012 in the United States alone (Siegel et al., 2012). Despite the progress made in the management of metastatic CRC (mCRC) over the last few years, with the incorporation in combination chemotherapy of two monoclonal antibodies targeting the epidermal growth factor receptor (Cunningham et al., 2004; Saltz et al., 2004; Van Cutsem et al., 2007) and the vascular endothelial growth factor (Hurwitz et al., 2004), the provided clinical benefit is modest and their long-term outcome is still unsatisfactory. The upfront administration of all active chemotherapeutic agents (the FOLFOXIRI regimen) has been tested, and its efficacy and tolerability was evaluated in two phase II studies, where the documented resectability rate (RR) was 58% and 69%, the time to tumour progression (TTP) was 13 and 10.4 months, and the overall survival (OS) 22.5 and 26.5 months, respectively (Falcone et al., 2002; Souglakos et al., 2002). In continuation, the same Greek and Italian groups, tested the FOLFOXIRI vs the FOLFIRI in two randomised trials (Souglakos et al., 2006; Falcone et al., 2007). Although the Italian study reported that FOLFOXIRI regimen was superior in terms of RR, progression-free survival (PFS) and OS (Falcone et al., 2007), this could not be demonstrated in the Greek trial (Souglakos et al., 2006). This discrepancy in the results of the two trials may be attributed to the different schedule and doses, differences in the inclusion criteria, as well as in the difference of OS in the control arm (19.5 and 16.7 months in the HORG and GONO, respectively). Conversely, it was demonstrated that FOLFOXIRI was associated with a higher resectability rate compared with FOLFIRI (Souglakos et al., 2006). In addition, the regimen was found to be more toxic for patients with performance status (PS) 2 and those aged > 65 years. Furthermore, in the young patients (65 years) FOLFOXIRI was found to be statistically significantly superior (RR 52.5% vs 32%) and with a favourable toxicity profile (Vamvakas et al., 2010). The common finding of the two trials was that FOLFOXIRI significantly increase the R0 secondary resections, which were triple in both trials: from 4 to 12% in the HORG trial and from 12 to 36% in the GONO trial (Falcone et al., 2007).

The addition of cetuximab to either FOLFIRI or FOLFOX led to an increased R0 secondary resection rate in KRAS wild-type patients, as it has been demonstrated in the randomised phase III CRYSTAL and phase II (OPUS) trials (Bokemeyer et al., 2009; Van Cutsem et al., 2009). On the basis of the above mentioned background, we conducted a non-randomised, open-label, pilot
phase II clinical trial to evaluate the activity and safety of FOLFOXIRI in combination with cetuximab as first-line treatment in young patients (<70 years old) with good PS (0–1) and unresectable mCRC.

MATERIALS AND METHODS

Patients and eligibility criteria

The study was open for patients’ enrolment from January 2007 to August 2010. Patients with histologically proven, KRAS wild-type unresectable mCRC, who have not previously received chemotherapy for metastatic disease, were eligible for the trial. Patients who had received adjuvant chemotherapy were eligible if they have remained free of disease for at least 6 months after the completion of adjuvant therapy. Other eligibility criteria were: age 18–70 years; PS (Eastern Cooperative Oncology Group) 0–1; at least one measurable lesion according to RECIST criteria; adequate haematologic parameters (absolute neutrophil count \( \geq 1.5 \times 10^9 \) per l and platelets \( \geq 100 \times 10^9 \) per l); creatinine and total bilirubin \(<1.25\) times the upper limit of normal (UNL); aspartate and alanine aminotransferase \(<3.0\) times the UNL; \(<5\) times in case of liver metastases existence; absence of active infection or malnutrition (loss of more than 20% of the body weight); and no history of a second primary tumour.

The protocol was approved by the ethics and scientific institutional and national committees. Patients were informed of the investigational nature of the study and provided their written informed consent before registration and participation.

Chemotherapy

Cetuximab was administered at a dose of 500 mg m\(^{-2}\) as a 2-h infusion on day 1 after pre-medication with histamine receptor antagonist and at least 1 h before the administration of chemotherapy. The administration of cetuximab every 2 weeks was recommended as previously described: irinotecan was administered at the dose of 150 mg m\(^{-2}\) as a 30-min i.v. infusion on day 1; LV was given at the dose of 200 mg m\(^{-2}\) as a 2-h i.v. infusion, followed by 5-fluorouracil (5-FU) 400 mg m\(^{-2}\) as i.v. bolus, and then 600 mg m\(^{-2}\) as a 22-h continuous i.v. infusion, on days 2 and 3; oxaliplatin was administered on day 2 at the dose of 65 mg m\(^{-2}\) as a 2-h i.v. infusion in parallel with LV, but using different lines (Souglakos et al., 2006). Treatment was administered every 2 weeks until disease progression or unacceptable toxicity, or until the patient declined further treatment. Cetuximab was continued until disease progression or unacceptable toxicity, even if chemotherapy had to be prematurely discontinued, or until the patient declined further treatment. For patients who were submitted to a secondary resection, a total of 6 months (12 cycles) of treatment was administered pre-operatively.

Patients were assessed for toxicity before each cycle of chemotherapy using the US National Cancer Institute’s – Common Toxicity Criteria, Version 3.0. Especially for cetuximab, if a patient experienced grade 3 skin toxicity, cetuximab therapy was delayed for up to two consecutive infusions without changing the dose level. If the toxicity resolved to grade 2 or less, treatment was resumed. In the case of a second occurrence of grade 3 skin toxicity, cetuximab therapy was delayed for up to two consecutive infusions with concomitant dose reductions to 400 and 300 mg m\(^{-2}\), respectively, which were permanent until completion of treatment. Cetuximab treatment was discontinued and the patient was withdrawn from the study if more than two consecutive infusions were withheld or if a fourth occurrence of grade 3 skin toxicity occurred despite appropriate dose reduction. Cetuximab therapy was not withheld for chemotherapy-related toxicities.

In case of allergic/hypersensitivity reactions, appropriate treatment measures were performed. Once the cetuximab infusion rate was decreased due to an allergic/hypersensitivity reaction, it remained decreased for all subsequent infusions. In case of a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion was stopped and the subject was removed from the study. In case of grade 3 or 4 allergic/hypersensitivity reactions at any time, cetuximab was discontinued.

Chemotherapy was delayed until recovery if neutrophils were less than \(1.5 \times 10^9\) per l or platelets less than \(100 \times 10^9\) per l, or for significant persisting non-haematologic toxicity. Doses of all chemotherapy agents were reduced by 15% in subsequent cycles in case of grade 4 neutropenia, or grade 3–4 thrombocytopenia lasting for more than 3 days, or in case of febrile neutropenia. Irinotecan and 5-FU doses were reduced by 15% in subsequent cycles in case of grade 3–4 diarrhoea. The 5-FU dose was reduced in grade 3–4 stomatitis or dermatitis. Oxaliplatin dose was reduced by 15% in case of persistent (\(\geq 14\) days) paraesthesia or temporary (7–14 days) painful paraesthesia, or functional impairment. In cases of persistent (\(\geq 14\) days) painful paraesthesia or functional impairment, oxaliplatin was omitted in subsequent cycles from the regimen until full patient recovery.

Patient evaluation

Pretreatment evaluation included medical history and physical examination, complete blood cell count with differential and platelet count, whole blood chemistry, determination of serum levels of carcinoembryonic antigen and computed tomography scans of the chest and abdomen, and had to be performed within 2 weeks before study entry. KRAS codon 12 and 13 mutations were analysed, at the time of patient’s registration, in microdissected samples from the primary tumour by standard Sanger sequencing as previously described (Saridaki et al., 2011). During treatment, a complete blood cell count with differential and platelet count was performed weekly, and in cases of grade 3–4 neutropenia, thrombocytopenia, or febrile neutropenia, it was performed daily until haematologic recovery. In addition, patients were clinically assessed, and routine biochemical tests were performed before each treatment cycle. Response to treatment was evaluated after four 2-week cycles (8 weeks) or sooner if clinically indicated.

Statistical considerations

The primary endpoint of the trial was the objective response rate (ORR) according to the RECIST criteria (Therasse et al., 2000), and the secondary endpoints were R0-RR, TTP, median OS (mOS), toxicity profile and pharmacogenomic analysis.

The study was designed as an exploratory, pilot, phase II study. We considered that if a response rate (complete and partial response) was observed in at least 60% (95% confidence interval (CI): 50–75.18%) in KRAS wild-type patients with wild-type KRAS, the regimen would merit further evaluation in prospective subsequent trials. The normal approximation method was used for the calculation of 95% CI. In addition, if one of the first 6 patients, receiving at least 70–80% of the planned doses died because of toxicity, the study would be discontinued, and depending on the reason of toxic death the protocol would be amended or permanently discontinued. The analysis of the primary endpoint was performed in the intent-to-treat population, defined as all patients who have been enrolled to the study.

Because of the exploratory nature of the study, mainly descriptive statistics were scheduled to be used. The probability of survival was estimated by the Kaplan–Meier method and the CIs were calculated using methods for exact binomial CIs.
Response duration was measured from the first documentation of response to disease progression. The TTP was determined as the interval between treatment initiation and the date when disease progression was first documented. Survival was measured from the date of registration to date of death. The follow-up time was measured from the day of first treatment administration to the last contact or death.

RESULTS

Patients' characteristics

The patients' characteristics and demographics are summarised in Table 1. The median age was 64 years (range, 36–70 years), 27 (90%) of the patients had a PS of 0, and the median number of target lesions was 1 per patient. Eighty per cent of the enrolled patients had received prior 5-FU-based adjuvant chemotherapy. The median time elapsed between the first diagnosis of metastases and study entry was 1.5 month (range, 0.4–2.0 months). All patients were evaluable for toxicity, and all, but one, were evaluable for response to treatment due to sudden death possibly related to treatment, and in the intent-to-treat analysis she was considered as having progressive disease.

Table 1. Patients' characteristics

| No of patients | % |
|----------------|---|
| Number of patients enrolled | 30 |
| Number of patients evaluable for toxicity | 30 |
| Number of patients evaluable for response | 29 |
| Age (Median (range)) | 64 (36–70) |
| Sex | |
| Male | 14 |
| Female | 16 |
| Performance status (WHO) | |
| 0 | 27 |
| 1 | 3 |
| Primary tumour location | |
| Colon | 22 |
| Rectal | 8 |
| Prior surgery | |
| Yes | 24 |
| No | 6 |
| Prior adjuvant chemotherapy | |
| Yes | 24 |
| No | 6 |
| Prior adjuvant RT | |
| Yes | 4 |
| No | 26 |
| Disease involved sites | |
| Loco-regional | 2 |
| Liver | 25 |
| Lymph nodes | 10 |
| Lung | 6 |
| Peritoneum | 2 |
| Other | 5 |
| Number of organs involved | |
| 1 | 17 |
| 2 | 8 |
| 3 | 3 |
| 4 | 2 |

Abbreviations: CR = complete response; PR = partial response; TTP = time to tumour progression.

Treatment efficacy

In an intent-to-treat analysis, documented complete and partial response were observed in 4 (13.3%) and 17 (56.7%) patients, respectively (overall response rate (ORR) = 70%; 95% CI: 53.6–86.4%). In addition, 8 patients (26.7%) had stable disease and 1 had progressive disease. The median time to initial documentation of response was 2 months (range, 2.0–34.0 months). The median duration of response was 7 months (range, 0.5–33.1 months; 95% CI: 5.5–8.5) and the median TTP was 10.2 months (range, 0.2–38.6 months; 95% CI: 7.1–13.4). After a median follow-up period of 31 months (range, 0.2–45.5), the overall median survival time was 30.3 months (95% CI: 18.8–41.9).

All patients included in the study had unresectable metastatic disease according to their treating physician and the evaluation of the surgeons in the University hospital of Heraklion. Sixteen of those patients presented metastatic disease confined to the liver, and the disease was unresectable due to extend to >60% of the liver parenchyma (11 patients) or technical reasons (5 patients). Secondary R0 resection was performed in 11 (37%) of these patients, 10 with lesions in the liver and 1 with lung metastasis (Table 2) without significant morbidity or mortality. Especially for patients with disease limited to the liver (n = 16), R0 resections were achieved in 10 patients, leading to an R0-RR of 62%. Five of the 11 patients with an R0 resection have relapsed after a median time of 10.2 months (range, 7–14.6 months) post-metastasectomy; after a median follow-up of 26 months (range, 13–37), all metastasectomised patients were alive at the time of analysis (Table 2). The resection was performed after four or eight treatment cycles in four and seven patients, respectively. Treatment was continued with the combination afterwards until the completion of 12 of the peri-operative treatment in all cases.

Treatment toxicity

The toxicity profile of the regimen is presented in Table 3. Diarrhoea and anaemia were the most common toxicities of the combination observed in 90% and 80% of the patients, respectively, followed by neutropenia (50%), fatigue (46.7%) and stomatitis (43.4%). Severe, grade 3 or 4 diarrhoea was observed in 16 (53%) patients. In most patients, anaemia was of grade 1 (43.3%) and 2 (33.3%). Grade 3 and 4 neutropenia was documented in 6 (20%) and 1 (3.3%) patients, respectively, whereas febrile neutropenia of grade 2 and grade 4 was developed in 2 patients (6.6%), each one requiring hospitalisation and i.v. antibiotics. Neurosensory toxicity was observed in 9 patients (30%). Cold-induced dysesthesia was reported in 7 patients (23.3%) and paraesthesia without pain in 2 (6.7%). Grade 3 rash was observed only in 1 patient (3.3%), whereas grade 1 and 2 in 10 patients (26.6%). Hypersensitivity reactions were observed in 9
patients and were, in general, mild. Hand-foot syndrome was detected in 6 patients (20%) but only 1 (3.3%) had grade 3. Four cases of infection were identified throughout the study. Five treatment-related admissions to the hospital were reported, all of them for severe diarrhea, whereas two of them also presented febrile neutropenia. There was one treatment-related death in a patient with disseminated peritoneal carcinomatosis, who developed grade 4 diarrhoea.

The analysis of the toxicity according to the gender revealed that vomiting was observed exclusively in females (P = 0.032), and neurotoxicity was more frequent in females (P = 0.047) (Table 4).

Compliance with treatment

At the time of this analysis, all 30 patients (100%) have discontinued treatment because of the following reasons: disease progression in 6 patients (20.0%), unacceptable toxicity in 5 patients (16.7%; 1 with grade 4 diarrhoea, 1 with grade 4 thrombocytopenia, 1 sudden death and 2 with an LOHP-related allergic reaction), patient withdrawal in 3 (10.0%), primary tumour surgical removal in 2 (6.7%) and completion of treatment in 14 (46.7%; 11 patients with secondary resection, who completed 6 months of peri-operative treatment, and 3 patients who were under treatment for more than 6 months at the time of study termination). In total, 300 courses of chemotherapy have been administered (median, 12 courses per patient; range 1–16). Seventy-one courses were delayed for a median of 7 days (range 3–56) because of haematologic (n = 12), non-haematologic (n = 20), and both haematologic and non-haematologic toxicity (n = 9), and 30 courses were delayed because of reasons unrelated to treatment or diseases. The median interval between cycles was 15 days (range, 15–19). Dose reduction was required in 38 cycles (12.7%) because of haematologic (n = 4 cycles; 1.3%) and non-haematologic toxicity (n = 26 cycles; 8.7%). Administration of GCSF was required in 36 cycles (12%) for the treatment of severe or febrile neutropenia. The delivered relative dose intensity was 85.3% for CPT-11, 93.2% for LOHP, 83.2% for 5-FU, 94.0% for LV and 94.4% for erbitux of the protocol-planned doses.
DISCUSSION

This is the second study investigating the relevance of cetuximab addition to FOLFOXIRI in the mCRC setting. In the current study the chemotherapy has been administered in fixed standard timeframe for each agent, whereas in the previous study it was administered in a chronomodulated fashion. We show that intensive chemotherapy with FOLFOXIRI plus cetuximab resulted in a particularly high response rate and a RR of 37%. Especially, for patients with liver-limited disease (LLD), which was initially unresectable, the R0-RR was 62%. Furthermore, after a median follow-up period of 31 months, our combination achieved an mOS time of 30.3 months.

Initial promising data demonstrated that cetuximab alone or in combination with irinotecan had clinical activity in irinotecan-refractory CRC patient (Cunningham et al, 2004; Saltz et al, 2004). Afterwards, the addition of cetuximab to chemotherapy regimens, such as FOLFIRI and FOLOX, was shown to increase RR, PFS and OS in the first-line setting (Bokemeyer et al, 2009; Van Cutsem et al, 2009). Furthermore, the addition of cetuximab to the triple combination of CPT-11/L-0HP/5-FU/LV administered under chronomodulation was the subject of the POCHER trial, which was recently published (Garufi et al, 2010). In this trial, cetuximab plus the chronomodulated triplet achieved 60% complete respectability of liver metastases (Garufi et al, 2010). The FOLFOXIRI regimen has been evaluated with the addition of bevacizumab in another phase II trial where the primary endpoint was the PFS, and bevacizumab was also administered as maintenance treatment (Masi et al, 2010). The results were deemed promising in terms of PFS and without the occurrence of unforeseen adverse events (Masi et al, 2010). Our results confirm the findings of the POCHER trial (Garufi et al, 2010) and extend those of the CELIM trial, in which the addition of cetuximab in either FOLFOX or FOLOFRI was evaluated in the neoadjuvant setting (Folprecht et al, 2005). The RR was 37% in the total population and 62% in LLD in the current study, 60% in POCHER trial (Garufi et al, 2010) and 38% for FOLFOX/cetuximab, whereas 30% for FOLFIRI-cetuximab in the CELIM trial (Folprecht et al, 2005). We documented a complete and partial response rate of 70%, which was 79% in the POCHER trial (Garufi et al, 2010), and 68% and 57% in the CELIM’s FOLFOX or FOLFIRI-cetuximab combination, respectively (Folprecht et al, 2005). Furthermore, the median TTP was 10.2 months in our patients’ population, whereas it was 14 months in the POCHER trial (Garufi et al, 2010), and the mOS in our study was 30.3 months after a median follow-up period of 31 months, whereas it was 37 months in the POCHER trial (Garufi et al, 2010). In addition, other studies have also, provided evidence of the effectiveness of cetuximab addition to a doublet combination in unselected mCRC patients, in terms of PFS and OS (Bokemeyer et al, 2009; Van Cutsem et al, 2009). In the OPUS and CRYSTAL trials, the addition of cetuximab to FOLFOX or FOLFIRI, respectively, led to increase of liver metastases RR, which was double in the cetuximab arm in both trials (Bokemeyer et al, 2009; Van Cutsem et al, 2009). In addition, another phase II study reported an impressive RR of 80.9% and an mOS exceeding 2 years (24.7 months; Assenat et al, 2011). Finally, the addition of panitumumab to FOLFOXIRI in KRAS-NRAS-HRAS-BRAF wild-type patients led to an RR of 89%, indicating that selection of patients based on multiple molecular markers should be evaluated in subsequent trials with this combination (Lonardi et al, 2012).

Toxicity was increased in our study with grade 3 or 4 diarrhoea and neutropenia reaching 53.3% and 23.3%, respectively. In the POCHER trial (Garufi et al, 2010), grade 3 or 4 diarrhoea was the major treatment toxicity documented in 95% of the patients, whereas similar incidence of diarrhoea was observed in the study of Assenat et al (2011). These findings indicate that the addition of cetuximab to three different schedules of FOLFOXIRI increases the incidence and severity of diarrhoea of the triple regimen. Dose reductions and/or modification were frequently required in all three studies, whereas in the POCHER trial an amendment with doses reduction was mandatory for the continuation and completion of the study. In addition, in the current and POCHER trials an increased gastrointestinal and neurosensory toxicity was observed in females. For these reasons, dose or schedule modification may be re-evaluated in future trials. In addition, the use of chronomodulated FOLOFOXIRI in the POCHER study limited the administration of this type of chemotherapy in experienced centres with the necessary equipment.

The addition to the triplet combination of a monoclonal antibody, this time bevacizumab, in an unselected patients’ population was recently published by Falcone et al (Masi et al, 2010). The RR was comparable to that of the present study, as well as with the that reported in POCHER trial (Garufi et al, 2010). The documented liver metastases RR of 40%, which was in the same rate with what was previously observed with the triplet alone (36%) by the same group, but less compared with ours (62%) and POCHER trial (60%; Garufi et al, 2010).

Potential limitations of our study are that it is a single-centre, non-comparative study, with a small number of patients enroled. Contrary, two strong points are, on the one hand the fact that the patients were selected on the basis of molecular markers and partly on physiological factors, as the enroled patients were younger than 70 years of age and with good PS. The benefit of the combination was greater than the potential risk, especially for the patients whose metastases became resectable after treatment, as it was associated with high response rates and facilitated metastasectomies in 37% of the enroled patients, providing promising survival results. In conclusion, the FOLOFOXIRI + cetuximab regimen presented interesting results with high response rate and R0 secondary resections in patients <70 years old, with good PS and limited number of target lesions (≤2), and merits further investigation, especially in patients with initially unresectable disease confined to the liver.

Conflict of interest

The authors declare no conflicts of interest.

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